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# NECROPSIES ON OKINAWANS

## Anatomic and Pathologic Observations

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### INTRODUCTION

THE NECROPSIES reported here as a contribution to racial and geographic pathology were done on Okinawans during the military campaign on Okinawa Shima. They were done to establish the causes of deaths, to obtain information on transmissible diseases borne by the natives which might endanger United States personnel and to collect data which might help to establish a base line from which any deviation induced in the incidence of diseases by the American occupation might be measured. Of special interest was the incidence of schistosomiasis, leishmaniasis, malaria, filariasis, yaws, leprosy, the acute enteric diseases, tsutsugamushi and Japanese encephalitis B. It became apparent early in the survey that some of the advance information on diseases occurring in the islanders needed modification. In general, health conditions were better than had been anticipated. During these necropsies some striking anatomic and pathologic differences from Americans and Europeans were observed, and they form an important part of this report. Such observations were of special interest when they suggested clues to the etiologic agents of the diseases concerned. The low incidence of disorders of the endocrine system and of degenerative diseases was especially impressive.

These examinations were made at a military government hospital from June 13 to July 30, 1945, inclusive. The patients had been evacuated from the front as it advanced to the southern end of the island. The majority were war casualties, but there were some with diseases not due to combat. They had been ill for periods ranging from several days to four weeks prior to being admitted to this hospital. Consequently, injuries which are soon fatal were seldom seen. On the other hand, most of the survey was made so soon after the campaign began that the full late effects which follow dislocation of a population by war had not yet developed.

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The racial origins of the Okinawans, never having been recorded, are obscure. It is believed that to the original Ainu (Caucasoid) people, found here as in the Japanese Islands, were added, many centuries ago, Chinese, Korean, Japanese and to a lesser degree Malay strains by invasion and immigration. There may be minor differences in origin of the people on different parts of the island, just as there are differences in culture and language (three dialects). The people reported on here came from the southern half of the island.

One hundred and fifty necropsies were performed, of which 51 were on males and 99 were on females, a ratio of 1 : 2. In age the subjects varied from 18 days to 95 years. All ages and sexes were well represented except that there was a relative paucity of men in the military age groups, they having forcibly or voluntarily joined the Japanese military forces.

TABLE 1.—*Distribution by Age and Sex*

| Age, Yr. | Males | Females | Total |
|---|---|---|---|
| 0 - 1 | 6 | 4 | 10 |
| 2 - 5 | 6 | 10 | 16 |
| 6 - 10 | 2 | 8 | 10 |
| 11 - 15 | 6 | 10 | 16 |
| 16 - 20 | 4 | 12 | 16 |
| 21 - 30 | 4 | 9 | 13 |
| 31 - 40 | 3 | 11 | 14 |
| 41 - 50 | 6 | 9 | 15 |
| 51 - 60 | 4 | 11 | 15 |
| 61 - 70 | 7 | 12 | 19 |
| 71 - 80 | 3 | 2 | 5 |
| 81 - 90 | 0 | 0 | 0 |
| 91-100 | 0 | 1 | 1 |
| Total | 51 | 99 | 150 |

Forty persons (26 women and 14 men) were over 50 years old, a point of importance when one comes to consider the incidence of neoplastic and degenerative diseases. Additional data on age and sex are presented in table 1.

## ANATOMIC OBSERVATIONS

The Okinawans are small, dark, Oriental people with good development and configuration of the body. Although they are usually classified as mongoloid, the implied resemblance is not pronounced. The epicanthic fold is generally inconspicuous or absent. And although they are classified with the yellow peoples, they are nearly all dark brown, probably due to Malayan blood and to prolonged exposure to the tropical sun, the majority being agricultural, rural and fisher folk. Rarely a person is seen who has a light skin but who otherwise resembles his neighbors. Such color is attributed by the Okinawans to European rather than to Ainu blood.

The average length of 26 men over 20 years of age was 153.8 cm. (60.5 inches); the minimum was 142 cm. and the maximum was 167 cm. The average length of 48 women of corresponding ages was 141.8 cm. (55.8 inches), with a minimum of 126 cm. and a maximum of 155 cm. The children were small so that at first there was a tendency to underestimate their ages by several years.

Body weights were not taken, but they appeared to be in good relation to the heights. Both sexes were well proportioned and muscular. Obesity was practically nonexistent, but many young women were plump. The thickest portion of the fat of the abdominal wall was generally under 10 mm. in women; it was rarely over 15 mm. In men the fat, subcutaneous and internal, was even less abundant.

The carriage was erect, and in the women, who commonly carried heavy burdens balanced on their heads, the gait was graceful. Both thorax and pelvis appeared to be relatively flat in the anteroposterior diameter. The legs were usually straight, and when they were not, they were slightly bowed; they were muscular and rather short. The feet were well developed and broad across the toes. The great toe was well developed, and it was usually separated from the second toe. Shoes were generally not worn, and toes were used for grasping in the weaving of ropes, baskets, and hats and in other handicraft.

In facial features the Okinawans varied between two extremes. Some were people with broad faces, thick lips, flat concave noses, rather thick skin and stocky bodies. Others had more delicate features, lower cheekbones, thin lips, thin, straight noses and slenderer bodies.

The hair was black, straight and soft and was less abundant on the average than that of Americans. In men it was generally moderately abundant on the scalp, the face, the axillas and the pectoral and pubic regions and scanty on the extremities. In women it was abundant on the scalp but scanty elsewhere, including the pubic region and the axillas. Hirsutism of the face, the arms and the legs was rare in women. The hair remained black into advanced ages; white hairs were rarely present in the early fifties, and practically all hairs remained black in some persons stated to be more than 70 years old. Baldness was rare.

The excellent muscular development of both sexes was apparent at a glance, but it was even more impressive on dissection. The pectoral and other muscles about the shoulders, the sternocleidomastoid muscle, the strap muscles about the thyroid gland and the other muscles of the neck, as well as the muscles of the extremities, and those about the spine, were exceedingly well developed, especially in the women. This was not surprising to any one observing the women digging in the fields or carrying heavy burdens on their heads as they trotted

along the paths and highways. Despite repeated childbirth, the abdominal wall tended to be flat and firm. Cystocele was observed in the perineum only twice and rectocele only once.

Internally, except for the small size of the viscera in conformity with the small body size, the most striking anatomic differences from Americans were found in the colon, the spleen, the pancreas and the biliary system. The colon was large, long and curiously tortuous. The cecum and the ascending colon were in the usual position, but at the hepatic flexure there was usually an S-shaped (S lying on its side) double curvature, with the three limbs of the S bound together by mesenteric folds. The center of the transverse colon lay low, usually sagging into the lower part of the abdomen. The splenic flexure, the descending colon and the rectum were normal, but the sigmoid flexure formed a long, large loop which frequently reached far into the right side of the abdomen. The explanation of this large, long tortuous colon was not certain. It was obviously an inherited characteristic, for it was already present in infants, in whom, however, it was less pronounced than in adults. The suggestion is made that it represents an adaptation to centuries of a predominantly vegetarian diet with its bulky fecal residue, analogous to that of herbivores.

Two noteworthy anatomic peculiarities were found in the biliary system: The gallbladder occasionally showed the fold and thickening of the distal end sometimes called "monk's hood." The common and hepatic bile ducts were frequently conspicuously larger than those of Caucasoid peoples. There was no evidence that this was due to disease.

The spleen was normally small. This reduction in size was out of proportion to that of the other viscera and to that of the body in general. On the other hand, the pancreas was relatively enlarged. It was firm and pale yellowish pink. Adipose infiltration like that commonly seen in the pancreas of Americans after middle age was seldom present, and the size, the color and the turgor were maintained into advanced ages. In adults of the United States the normal spleen is heavier than the pancreas, but in these Okinawans the normal pancreas was about one-third heavier than the spleen because of the relative enlargement of the former and the reduction of the latter.

### CAUSES OF DEATH

Death was due to combat injuries in 100 cases, to noncombat (chiefly medical) causes in 36 and to a combination of war injuries and medical conditions in 14.

The combat injuries that caused death of 100 persons can be classified as follows: gunshot and shrapnel wounds, 88 persons; burns,

3; effects of inhaling chemical fumes, 9. Some additional persons who died of other causes showed nonfatal injuries of the three types mentioned; 14 had nonfatal gunshot and shrapnel wounds, 8 nonfatal burns and 1 showed effects of inhalation of chemical fumes.

Of the 88 persons with fatal gunshot and shrapnel wounds, over half (45) had multiple wounds. The number of such wounds per person is given in table 2. The number of major injuries borne by these people was at times astounding.

TABLE 2.—*Number of Gunshot and/or Shrapnel Wounds per Person in Eighty-Eight Fatal Cases*

| Wounds per Person | Cases |
|---|---|
| 1 | 43 |
| 2 | 19 |
| 3 | 8 |
| 4 | 5 |
| 5 | 3 |
| 6 to 10 | 5 |
| 11 to 25+ | 5 |

In table 3 are given the locations of the fatal gunshot and shrapnel wounds in 88 persons and the ultimate cause of death in these persons. The chief cause of death was infection of wounds, usually with generalization of the infection or its toxic products. A specific type of infection,

TABLE 3.—*Location of Gunshot and/or Shrapnel Wounds in Relation to Cause of Death in Eighty-Eight Cases*

| Cause of Death | Cases with Given Location of Wound | | | | | |
|---|---|---|---|---|---|---|
| | Soft Tissues | Thorax | Abdomen | Skull | Other Bones | Total |
| Toxemia, septicemia, pyemia, empyema or abscess | 10 | 3 | 4 | 4 | 14 | 35 |
| Tetanus | 10 | 1 | 0 | 0 | 20 | 31 |
| Hemorrhage | 3 | 2 | 4 | 0 | 0 | 9 |
| Gas gangrene | 3 | 0 | 0 | 0 | 4 | 7 |
| Pneumonia | 0 | 1 | 0 | 1 | 2 | 4 |
| Shock | 0 | 0 | 0 | 0 | 1 | 1 |
| Urinary retention | 0 | 0 | 0 | 0 | 1 | 1 |
| Total | 26 | 7 | 8 | 5 | 42 | 88 |

namely tetanus, was fatal in 31 persons and was present in a recovery stage in an additional one. Shock and hemorrhage stand low as causes of death in this series because most of the patients evacuated to this hospital had been injured several days or even several weeks before admission. The wounds were usually in poor condition when the patients entered the hospital; many teemed with maggots.

The causes of death in 36 noncombat cases were as follows:

| | |
|---|---|
| Malnutrition and pneumonia | 10 |
| Pneumonia (lobar 2, bronchial 4) | 6 |
| Tuberculosis | 5 |
| Dysentery (amebic 4, bacillary 1) | 5 |
| Cirrhosis of the liver | 2 |
| Toxemia of pregnancy | 1 |
| Typhoid | 1 |
| Heart disease (beriberi?) | 1 |
| Senility | 1 |
| Prematurity and fetal atelectasis | 1 |
| Skull fracture | 1 |
| Operative (noncombat) sequels | 1 |
| Uncertain | 1 |

Although they are classified as noncombat cases of death, the accuracy of this classification could be challenged, since in a number of them, no doubt, death was indirectly due to the war. This is particularly true of cases of death from malnutrition and pneumonia; death from these causes was observed predominantly in infants and children, some of whom had a history of existence in caves under adverse conditions. There was, however, no way of evaluating this factor more accurately.

The unfavorable influence of an injury on an infection, and vice versa, is illustrated by the 14 cases in which a war injury and a noncombat condition combined to cause death. These cases were as follows:

| | |
|---|---|
| Gunshot or shrapnel wounds and dysentery | 7 |
| Gunshot or shrapnel wounds and tuberculosis | 5 |
| Gunshot or shrapnel wounds and filariasis | 1 |
| Burns and tuberculosis | 1 |

### CONGENITAL MALFORMATIONS AND ANOMALIES

Although congenital defects seemed to be more common than in America, only one, horseshoe kidney, was of clinical importance. In addition to the small size of the spleen previously mentioned, this organ showed a high incidence of multiple congenital clefts. Observations were recorded in 111 cases, in 2 of which no clefts of the spleen were seen; in 109 cases the spleen had from one to nine clefts, as follows: in 32, two clefts; in 24, three; in 18, four; in 11, five; in the remainder (24 cases), from six to nine. The clefts were usually shallow, but occasionally they were so deep as to nearly subdivide the organ. Accessory spleen, which probably represents a further degree of this malformation, was common. It was observed in 17 of 150 necropsies. In 4 cases two accessory splenules were seen.

Horseshoe kidney, hypoplasia of a kidney and double ureters were each found once. In 2 cases a diverticulum of the urinary bladder was encountered.

Abnormal numbers of pulmonary lobes were fairly common. One right lung had four lobes, and five right lungs were bilobed. Two left lungs were unilobed. In 1 case a lung showed multiple cysts, probably congenital.

The main peculiarity seen in the alimentary tract was the enlargement and tortuosity of the colon previously described. Meckel's diverticulum and a diverticulum of the jejunum were seen in 1 case each, and diverticula of the duodenum in 3 cases. Pseudodiverticula of the colon, so common in some parts of the world as acquired abnormalities, were not found in these Okinawans. Many persons with harelip and crossed eyes were seen in passing through the villages, but statistics on the incidence of these anomalies are not available.

One undescended testis was seen, and one axillary mammary gland. The ovaries were occasionally greatly elongated and cylindric, although small.

Two hearts showed patent foramen ovale. One liver had multiple cysts.

### INTESTINAL HELMINTHIC INFECTIONS

Fifty-three persons had no recognizable intestinal helminths, but 97 (64.7 per cent) had one or more types. Ascaris was found in 67 of these persons (44.7 per cent), hookworm in 52 (34.7 per cent), and Enterobius and an unclassified tapeworm in 1 each. The incidence of infection was somewhat greater than is indicated by these figures, especially with respect to the small types of worms, as is shown in the following paragraph.

Because some of the intestines showed postmortem color changes or because the worms were scarce, hookworm infection was sometimes not recognized. The magnitude of this negative error was determined by comparing in 72 cases the results of gross inspection for worms with those of microscopic examination of the feces taken from the lower part of the colon for ova (performed by Lieutenant (jg) T. W. Simpson [M.C.] U.S.N.). The deficiency in the gross diagnosis of hookworms was found to be over 10 per cent. Even greater negative errors were found with respect to the other small intestinal helminths during this microscopic check on the macroscopic necropsy observations. Thus, in the course of the 72 microscopic examinations of feces, ova of Trichuris were found thirteen times, ova of Enterobius twice and larvae of Strongyloides twice. The hookworms were most commonly found in the upper part of the jejunum, where they clung to the mucosa, but at times they were found from the duodenum to the colon.

Ascaris was found in 67 cases (44.7 per cent). They were most common in the small intestine, where they sometimes formed coiled masses, but they were seen in all parts of the alimentary tract, from the mouth to the anus. The largest worm measured was 32.5 cm. Their numbers varied from 1 to 50. These numbers are shown in table 4.

TABLE 4.—*Number of Ascarids per Person in One Hundred and Fifty Cases*

| Ascarids per Person | Cases |
|---|---|
| 0 | 83 |
| 1 | 26 |
| 2 | 12 |
| 3 | 5 |
| 4 | 7 |
| 5 | 1 |
| 6 | 4 |
| 7 | 3 |
| 8 | 2 |
| 9 | 1 |
| 16 | 1 |
| 17 | 1 |
| 18 | 2 |
| 19 | 1 |
| 50 | 1 |

The diagnosis of ascariasis obtained by examining the alimentary tract for worms of Ascaris was found to be more reliable than that obtained by examining the feces for ova in the 72 cases previously mentioned in which this comparison was made. This is explained by the fact that many persons (26) had only one worm and that others had only two or three. In cases in which all worms were males or nongravid females, diagnosis by examining the feces for ova was not possible.

There were no known pathologic complications arising from the activities of any of these worms.

## NEOPLASMS

Malignant tumors were not encountered in this series of 150 necropsies. This paucity of cancers may be significant in view of the fact that 40 of these people were over 50 years old.

Benign neoplasms, on the other hand, were fairly numerous. The following types and numbers were found:

| | |
|---|---|
| Lipoma (jejunum 4, adrenal gland 1) | 5 |
| Adenomatous polyp (colon) | 1 |
| Leiomyoma (stomach 2, ileum 2, duodenum 1) | 5 |
| Benign epithelioma of skin | 2 |
| Dermoid of ovary | 1 |
| Lymphoma of ileum | 1 |
| Uterine fibroids | 1 |
| Endometrial polyps | 2 |

The observation that only 1 uterus among 54 from women over 20 years of age had fibroids is noteworthy. One uterus had been removed for unstated causes; the patient bore the only laparotomy scar in the entire necropsy series.

### INFECTIOUS DISEASES

*Tuberculosis.*—Advanced tuberculosis was seen in 11 persons. Three of these were males, and 8 were females. Their ages were from 3 to 50 years. The tuberculosis was predominantly pulmonary in 10; calcification of lymph nodes due to tuberculosis (tabes mesenterica) was present in 1, a child 3 years old. In 5 persons the tuberculosis appeared to be the sole cause of death, but in the remaining 6, although the tuberculosis was equally advanced, there were also significant gunshot or shrapnel wounds (in 5) or chemical and heat burns (in 1). The tuberculosis was always extensive. It was acute in all instances except 1, in which fibroplastic pulmonary scarring was found in addition to acute caseous tuberculosis and areas of tuberculous pneumonia. The examiner had not seen in the United States a series of 11 consecutive cases of tuberculosis with such acute and extensive lesions. The acuteness of the lesions together with the absence of fibroplastic processes strongly suggested that these infections were recently acquired. The extrapulmonic tuberculous lesions which were present in the pleura, the lymph nodes, the larynx, the lower intestine, the adrenal glands, the spleen and other organs in these cases were not different from those commonly seen in America in cases of acute advanced pulmonary tuberculosis. Disseminated miliary lesions were present in 2 instances.

Subclinical tuberculous infection, minimal or inactive, was found as an incidental lesion in 24 cases; both the primary type and the reinfection type were observed. The primary type occurred with pulmonary tubercles in 9 cases, with tubercles of tracheobronchial lymph nodes in 5 cases and with both in 3 cases; minimal active pulmonary tuberculosis of the reinfection type was noted in 4 cases. Twenty of the patients with subclinical infection were females, and 4 were males; 14 were over 50 years old.

The total incidence of tuberculous infection found in these necropsies was 23.3 per cent, of which 7.3 per cent was advanced and 16 per cent minimal or inactive. The latter figure would be considered low for postmortem examinations in the United States. No data on the relative number of positive tuberculin reactors are available, with which these anatomic data might be compared. It is interesting that two types of lesions which are considered to be evidence of past tuberculous infection and which are commonly seen in the United States were never or seldom seen in these Okinawans: Thickened, puckered scars in the apical pleura were never seen. Focal fibrous pleural adhesions in

relation to subpleural lesions were rarely found at the apexes of the lungs, although adhesions were common elsewhere.

The inference from these two observations is that either the incidence of tuberculous infection was low among these people or the infection of some of them was so slight as to leave insignificant anatomic residues. On the other hand, when tuberculosis gained a foothold, as it did fairly often under war conditions, it tended to be acute and massive. This may be a course induced by the adverse environmental factors incidental to the war, such as malnutrition, overcrowding with strangers in caves, and physical exhaustion, or it might indicate a low racial immunity.

*Tetanus.*—Thirty-two of these persons had tetanus. One recovered from tetanus but died of pulmonary tuberculosis. Thirty-one died of the tetanus, although 2 of them had nearly recovered from it only to succumb to complications, namely, pulmonary abscesses, which were probably the result of faulty deglutition during the stage of severe tetanus. Tetanus was found at ages from 2 to 62. Its distribution by sex was in the same proportion as that of the entire necropsy series. In all cases it was caused by gunshot or shrapnel wounds, which were single in 15 persons and multiple in the remainder. Three persons with tetanus had over 10 wounds each. Many of the wounds involved one or more bones; others were in soft parts only. The tetanus made its appearance between the sixth and the twenty-first day, inclusive, after injury. There was no relation between the location of the injury and the period of incubation of the tetanus. The time of survival after the clinical onset was usually between twenty-four and forty-eight hours. The minimal period of survival was twelve hours. One person made a complete recovery from tetanus in twenty days but died later of tuberculosis; another had nearly recovered in ten days, and a third had recovered by the eighteenth day except for bilateral foot drop. The last 2 persons succumbed to pulmonary abscesses.

A constant gross finding in persons who died of tetanus was an obviously infected wound without, however, massive suppuration. The changes in the viscera also presented a constant picture, but they were not pathognomonic of the disease since they resembled those found in other forms of acute toxemia. These changes included: moderate to massive pulmonary hyperemia and edema, dilatation of the right ventricle, cloudy swelling of the heart, the liver and the kidneys, and slight acute hyperplasia of the spleen. The central nervous system grossly appeared normal in every case. The diagnosis of tetanus was made clinically and was confirmed by the gross pathologic changes and occasionally by culture of material taken from the wound.

*Gas Gangrene.*—Seven patients died of gas gangrene which developed as a result of shrapnel or gunshot wounds. Another person with gas

gangrene of the foot survived amputation of the foot only to contract tetanus five days later and succumb to this infection. Gas gangrene occurred in both sexes and at ages ranging from 4 to 63 years. No unusual features were recognized in this disease.

*Rheumatic Fever.*—The only recognized manifestation of rheumatic infection was observed in the hearts of 4 persons. In 2, a man aged 55 and a woman 42 years old, both of whom died of infected shrapnel wounds, minimal scarring of the cusps of the mitral valve and of the adjacent chorda tendineae was noted. In neither was there any change in the heart or elsewhere as evidence of functional effects. The third patient, a woman aged 20 who died of tetanus, had thickening and fusion of the mitral cusps, a thrombotic vegetation on one mitral cusp, thickening of the endocardium of the left atrium and slight hypertrophy of the right ventricle. Another woman, 55 years old, who died of extensive penumonia, had a history of cardiac decompensation of one year's duration. She had high grade mitral stenosis and both stenosis and insufficiency of the aortic valve, small thrombotic vegetations on both valves and moderate cardiac hypertrophy.

There was good evidence that rheumatic endocarditis occurs in some of these people and that the cardiac lesions resemble those seen in the United States, but the incidence of this involvement remains to be determined, although it appears to be low.

*Bacterial Endocarditis.*—Bacterial endocarditis was found in only 1 person, a woman aged 64, in whom peritonitis and pyemia with multiple abscesses of viscera developed following a shrapnel wound of the abdomen. On one cusp of the tricuspid valve a shaggy vegetation was found, measuring 14 by 12 by 2 mm.

*Syphilis.*—Evidence of syphilis was found in only 1 necropsy. A man aged 69 died one month after sustaining a large shrapnel wound of the thigh, which had become infected. His aorta showed typical syphilitic involvement with diffuse dilatation of the ascending portion of the arch. The aortic ring and valve and the coronary ostiums appeared normal.

*Filariasis.*—Death from filariasis was not demonstrated in this series of necropsies. The incidence of infection as indicated by microfilarias in the blood is known to be high among Okinawans, but elephantiasis is not common. Thirteen persons showed anatomic changes characteristic of filariasis. Twelve were men. All were over 50 years of age except 2 who were both 30. The commonest lesion, found eleven times, was chronic inguinal lymphadenitis; sometimes it was associated with similar changes in the femoral or the iliac lymph nodes. Hydrocele was usually present in these men; it was unilateral in 6 and bilateral in 4. In 1 man and 1 woman the inguinal lymphadenitis was associated with elephantiasis of both legs, of a moderate degree. One man had extensive

lymphangiectasis and lymphadenopathy of the periaortic abdominal and pelvic lymphatic system of unknown but possibly filarial cause.

*Dysentery.*—The acute ulcerative lesions of dysentery were seen in the terminal part of the ileum or in the colon or in both in 16 necropsies. In 5 cases the dysentery was thought to have been the cause of death, in 7 it was considered contributory to death, and in 4 it was thought to be an incidental finding. The etiologic classification of these cases, based in large part on the gross pathologic appearance of the bowel and corroborated by further laboratory studies in only a few cases, was as follows: amebic dysentery, 6 cases; bacillary dysentery, 5 cases; dysentery of uncertain cause, 5 cases.

*Pneumonia.*—Pneumonia was seen in 47 necropsies. Primary lobar pneumonia was found twice, primary bronchopneumonia four times, secondary bronchopneumonia thirty-seven times and chemical pneumonia four times.

*Fibrous Pleural Adhesions.*—Fibrous pleural adhesions were found in 81 persons (54 per cent). They were bilateral in 37, on the right side in 26, and on the left in 18. In extent they varied from focal presence of fibrous bands to total obliteration of the pleural cavity. The incidence was approximately equal in the two sexes. Adhesions were already present in 3 infants aged 2 years. The incidence increased sharply in children up to the age of 10 years; in persons more than 10 years of age it was 61.4 per cent, and in those more than 50 years of age it was 77.5 per cent. Adhesions were seldom found at the apexes of the lungs and, because subpleural tubercles were uncommon, they were not often found in relation to peripheral tubercles. The cause would appear to be other than tuberculosis.

*Miscellaneous Infections.*—Typhoid was found in 1 person, a girl 8 years old.

No proof of gonococcic infection was found on gross examination in these necropsies. In males there was no urethral stricture, prostatitis, epididymitis or testicular atrophy. Women appeared to be remarkably free from infection of the uterine cervix despite the fact that many of them were multiparous. Chronic pelvic inflammatory disease was found only a few times, and then with little to suggest that it was gonococcic.

There was no postmortem evidence of malaria, and this was in agreement with the clinical and hematologic evidence in these people at this particular time. No malarial pigment was seen in the spleen, the lymph nodes or the liver, and there were no splenic enlargements, acute or chronic, not readily explainable by other causes. In fact, the spleens, as previously mentioned, tended to be amazingly small. Smears from some spleens were examined for malarial parasites and invariably disclosed none.

There was no evidence of Trematode, or fluke, infection of the blood, the liver, the intestine or the lungs.

The only evidence suggestive but by no means diagnostic of leishmaniasis consisted of large areas of cutaneous depigmentation in 2 old men.

Yaws, leprosy, tsutsugamushi and Japanese encephalitis B were not seen in these necropsies.

### RETROGRESSIVE, DEGENERATIVE AND SENILE CHANGES

*Senility.*—The onset of senile changes in Okinawans is delayed until advanced ages, and the complete picture comes even later. The first bloom of youth is early lost, especially in women, but thereafter the aging process appears to be slow, and guesses as to their ages are inaccurate. In the necropsies the picture was complicated by the presence of some malnutrition consequent to the war, so that the turgor of tissues and the amount of subcutaneous fat were unreliable indexes of age. The following criteria were found to be more reliable: atrophy of skeletal muscle and especially of cardiac muscle; percentage of white hairs among the black, all regions of the body being taken into account; calcification of the costal cartilages; skeletal changes; arteriosclerosis; atrophic pulmonary emphysema and "barrel chest." Judged by these criteria, many of the people were remarkably well preserved in the late sixties. Good posture was, on the whole, maintained among the old people. A few showed external deformity at joints but in those whose joints were examined by dissection there were minimal corresponding skeletal changes.

*Cardiovascular System.*—The relative freedom of these Okinawans from degenerative diseases of the cardiovascular system was amazing. Hypertensive heart disease and malignant nephrosclerosis were not seen. Sclerosis of the aorta was found in 7 bodies, the stated ages of which were: 55, 60, 65, 70, 71 and 95 years. Only the 95 year old subject was a female. The severity of the sclerosis was graded from 1 plus to 2.5 plus (on the basis of 4 plus as a maximum). The sclerosis was chiefly fatty and hyaline, but one or more calcified aortic plaques were seen in 4 cases. The middle-sized arteries usually showed only tortuosity. Only 1 case of coronary sclerosis with calcification was found; in addition there were 5 cases of slight noncalcific coronary sclerosis. In no instance were any of the serious complications or sequels of arteriosclerosis seen in the heart, the brain or the kidneys.

The heart appeared remarkably well preserved at all ages. It rarely showed senile atrophy and then only at an advanced age and to a slight degree. In women up to 70 years of age the heart was usually large and healthy appearing. Infiltration of the myocardium, particularly of the right ventricle, by adipose tissue from the epicardium, which is so

common in older women in some parts of the world, was not seen at all in these Okinawans, in conformity with their lack of obesity elsewhere and their ability to perform hard physical work. Myofibrosis of a degree visible grossly was seen only twice. Once it was found in relation to a slightly sclerotic but not occluded coronary artery, and once it appeared as an isolated cardiac lesion. Cardiac hypertrophy of the hypertensive type was seen only once; then it was associated with toxemia of pregnancy. Coronary occlusion was not found in these necropsies.

Only 3 cases of heart disease of known clinical significance appeared in this series of cases. One patient was a woman suffering from toxemia of pregnancy; she died in acute cardiac failure seven days post partum after refusing to stay in bed. The second patient was a woman aged 55 who died of extensive lobar pneumonia after having suffered from progressive heart failure for about one year, due to chronic mitral and aortic stenosis and insufficiency of the rheumatic type. The third patient was a man aged 71 who for three months had advanced cardiac decompensation, from which he died. He had practically no arteriosclerosis, and the cause of the heart disease was obscure, although the possibility of beriberi was considered.

*Respiratory Tract.*—Atrophic emphysema was seen occasionally in some of the older people. In its advanced stages it was accompanied by "barrel chest."

*Gastrointestinal Tract.*—Acute gastric ulcers were seen in 2 women, aged 46 and 70 years, both of whom had bacillary dysentery and infected shrapnel wounds, which did not involve any bones or the head. Another woman, 35 years old, who had extensive second and third degree burns from a flame thrower had five gastric ulcers and one duodenal ulcer, all acute. These ulcers were incidental postmortem findings.

Most of the appendixes appeared comparatively normal. In no person had the appendix been surgically removed. One appendix was 1 cm. long and terminated in a slender fibrous cord. Another was involved by an extensive acute ulcerative process of the ileum and the colon which had perforated, causing peritonitis.

The colons, except for the tortuosity, the acute ulcerative lesions and the few benign tumors previously mentioned, appeared normal. The fecal contents were usually soft and voluminous. In no case were multiple pseudodiverticula seen of the type so commonly found in the colons of people in the United States.

*Liver.*—Fibrous peritoneal adhesions were often present on various surfaces of the liver without appreciable thickening of the hepatic capsule elsewhere.

Cirrhosis of the liver appeared to be a common disease. It was found in 2 men and 4 women, who were between the ages of 47 and 70. In 3

of these persons the cirrhosis was mild, coarse and irregular in type; in the other 3 it was advanced, producing portal obstruction and causing death of 2. In 2 persons the liver was of the multilobular, irregular type; it was enlarged in one and reduced in size in the other. One small liver showed advanced cirrhosis of a monolobular type, with little evidence of regeneration.

*Biliary System.*—Remarkably little disease was found in the biliary system. The most striking abnormality was the enlargement of the ducts previously described, considered to be normal. Chronic cholecystitis with marked thickening of the gallbladder wall was seen once. A solitary smooth oval gallstone, 21 mm. in greatest diameter, was found in a woman aged 61. Another woman, aged 56, had 18 small faceted stones, each about 7 mm. in diameter. Cholesterosis of the mucosa of the gallbladder was seen three times.

*Spleen.*—The spleen was normally small in these people. In senility and malnutrition it underwent atrophy in accordance with that of the other viscera. It showed acute hyperplasia in the presence of some infections, and chronic splenomegaly was observed in several cases of generalized chronic passive congestion and in cases of hypertension of the portal system associated with cirrhosis of the liver. No malarial pigmentation was recognized.

*Lymphatic System.*—The most conspicuous and consistent change in the lymphatic system was hyperplasia of the mesenteric lymph nodes, present in about 90 per cent of these persons. It was more pronounced in the young than in the old. The degree of enlargement was usually 1 or 2 plus (on the basis of a maximum of 4 plus). The nodes were discrete, elastic and pale yellowish gray; there was no periadenitis. The cause of this mesenteric lymphadenitis was not determined, but it appeared to be related to the intestinal helminthic infections which were so common.

The tracheobronchial lymph nodes showed less than the expected incidence of enlargement, because of the low incidence of tuberculosis in these nodes. The inguinal, femoral and iliac lymphadenitis related to filariasis has been described with that disease.

*Skeleton.*—Except for the traumatic injuries, no major pathologic conditions were seen in the skeletons of these people.. The commonest retrogressive abnormality was softening of bones, noticed especially in the sternum and the ribs, so that they bent and fractured easily, although incompletely. This type of osteomalacia and osteoporosis was present thirteen times. It was found equally in both sexes and occurred after 50 years of age with two exceptions (30 and 44 years). It accompanied malnutrition, wasting diseases and senility. A differentiation between osteoporosis and osteomalacia was not made.

Osteoarthritis of vertebral bodies, so common in Americans over 50 years old, and characterized by a small amount of "lipping" in the lumbar or the thoracic regions, was seen only nine times and then as an incidental postmortem finding. It was always of a mild degree. All the subjects were over 50 years of age, and the sexes showed an equal incidence. Deforming arthritis of several joints of one hand was seen in a woman 52 years old.

The costal cartilages were not calcified even in the aged.

The teeth were generally good until middle age, after which they deteriorated rapidly. Young people frequently had gold crowns or half crowns on four upper front teeth, but these had been placed on sound teeth as an aid to beauty.

*Endocrine System.*—The pancreas showed no recognizable pathologic changes. It was large, firm and pale yellowish pink. Even in the aged it failed to undergo atrophy, and there was little or no tendency toward adipose tissue infiltration and replacement. There were no known cases of diabetes in this series, and glycosuria was not seen in the clinical laboratory during this time.

The thyroid gland was small, pale tan to pale yellowish brown, firm and without any nodules except in 2 instances in which it showed small colloid cysts. Each person had only a few grams of thyroid tissue.

The thymus gland was not remarkable except that, because of the small amount of mediastinal fat, it was easily seen.

The adrenal glands were characterized by their large size in proportion to that of the body. They were large even in cases of severe malnutrition. They contained no visible areas of nodular cortical hyperplasia.

*Generative Organs.*—The prostate gland was usually small and symmetric. Nodular hyperplasia was seen in only 2 elderly men, aged 65 and 73 years. The enlargement was slight in each and had not produced any obstruction.

The seminal vesicles and the testes presented no noteworthy changes.

The uterine cervix was remarkably free from lacerations, erosions and chronic infection despite known child bearing. Uterine fibroids were practically nonexistent, only 1 uterus, from a woman 43 years old, showing multiple small tumors. Two uteri contained small endometrial polyps. The fallopian tubes, except for several with cysts and adhesions, were not abnormal. The ovaries commonly had small cysts. The mammary glands were not large, but the glandular tissue was abundant and the adipose tissue scarce. No cystic disease was found, and inspissated secretion was never seen in the ducts.

*Urinary Tract.*—Renal disease was extremely uncommon in these necropsies. One congenitally hypoplastic kidney was seen in a 9 month

old infant, but not a single contracted kidney, primary or secondary, was found. Coarse, retracted scars on the greater curvature, considered by some to follow arteriosclerosis and by others to represent pyelonephritic scarring, were seen only three times. Acute urinary retention, unilateral or bilateral and with or without infection, was the most common pathologic condition noted. It complicated injuries which involved the lower part of the urinary tract. Two cases of mild glomerulonephritis were recognized.

Calculi were found in the urinary tracts of 2 persons. One stone was found in the renal pelvis of a girl aged 9, who died of a shrapnel wound with an infected compound comminuted fracture of the femur and advanced pulmonary and miliary tuberculosis. A woman 42 years old, who died of exactly the same causes, had two yellowish brown concretions in one of the renal pelves. They had been wounded five and six weeks, respectively, before death, and the woman, at least, is known to have been treated with sulfadiazine.

*Tattooing.*—Tattooing of the backs of the hands as a form of branding at the time of marriage was practiced some years ago. The youngest woman showing these blue marks was 50 years old. Of 26 women over 50 years of age, 18 showed tattooing. It was seen in its most elaborate form in the very old women, in whom it sometimes extended from the distal phalanges of the fingers to the upper margins of the wrists. In its mildest form it consisted of blue dots up to 10 mm. in diameter over the middle articulation of the great finger and the adjacent third finger of each hand.

## MALNUTRITION

Malnutrition, of apparently recent origin, was seen a number of times and in all age groups. It appeared to be a factor contributory to death in a number of instances. In some cases there was a history of inadequate intake of food before admission to the hospital. However, the diet of these people prior to the invasion appears to have been excellent as judged by the absence of deficiency diseases, by longevity and by the stated and observed high fertility. It did not appear to promote rapid growth in the children, although they appeared well formed, had good teeth and were not pot bellied.

The diet formerly consisted mostly of carbohydrates, with sweet potatoes, rice and various vegetables predominating. The intake of fats was low, and the protein content of the diet appeared to have been deficient, although it probably actually was not. Proteins were chiefly vegetable in origin (soybeans). Meat was eaten infrequently, and little milk was used. Pork, fish and goat were the chief meats. Fruits were grown on a small scale. In the hospital the patients preferred their native diet of rice balls and sweet potatoes to American food, although

in all fairness it must be stated that they were judging the American diet largely by K rations.

At necropsy the chief evidence of malnutrition apart from emaciation was edema. It was thought to be a nutritional edema because it occurred in persons who had normal-appearing hearts and kidneys, who had little or no evidence of passive congestion and who often had a history of recent inadequate intake of food. Furthermore, this type of edema, which was seen only a few times during the first weeks of this survey, underwent a marked increase during the last weeks. It was seen nineteen times—twelve times in the last 22 necropsies.

Lieutenant (jg) T. W. Simpson studied the blood plasma protein levels in nearly 50 Okinawans who had edema and ascites in the absence of demonstrable cardiac or renal disease. He found the plasma proteins to be as low as 2.5 Gm. per hundred cubic centimeters, with an average of 4.5 Gm. The patients with an advanced degree of edema and anasarca made a poor response, if any, to the protein added to the diet or even to injected serum albumin, but those with a milder degree of edema showed a good response to the dietary treatment. He also found that most of these patients had microcytic hypochromic anemia.

### INFORMATION OBTAINED FROM OKINAWAN PHYSICIANS

Because the number of necropsies was small, the possibility existed that the sampling was not representative and that unwarranted conclusions were made, despite the fact that the findings were in agreement with those of Benjamin.[1] Furthermore, certain nonlethal diseases, as well as those present on the island only intermittently, even though in severe epidemic form, might be overlooked in a quick survey of this type. Evidence of another type which might corroborate, refute or supplement that obtained at necropsy was therefore desirable. This was systematically obtained from native Okinawan physicians.

A questionnaire was prepared, which covered over a hundred diseases, with particular emphasis on incidence, etiologic factors and importance. In interviews these questions were put to eight Okinawan physicians, who had practiced for periods varying from eight to forty-one years. With one exception they had attended medical school in Japan. They were found to be well informed, especially with respect to the infectious diseases. They had had large practices in the following towns: Shuri, Naha, Itoman, Miyazato, Haenna, Awasi and Sashiki. Their answers were recorded during the interview. When answers were reviewed, it was found that their opinions on medical matters agreed remarkably well but that there was some lack of agreement in answers to questions asked at the same time with regard to other fields. Necropsies were formerly done only occasionally, on order of the police. In the prefectural hospital at

1. Benjamin, E. L.: U. S. Nav. M. Bull. **46**:495, 1946.

Naha they were done at the request of physicians. There is no religious prohibition of such examinations, but the great reverence in which the dead are held and worshipped discourages wide practice of necropsy.

So far as it could be compared, the information obtained by the two methods, namely, necropsy and questioning of physicians, was in agreement, with two notable exceptions. Nephritis, type undetermined, was stated to be common, especially in children and very aged persons, among whom, it was said, the mortality due to this condition was low. At necropsy, on the other hand, the kidneys showed little evidence of past infection or of vascular disease. The other outstanding discrepancy concerned the cases of dysentery. The physicians stated that in practically all cases dysentery was amebic, whereas at necropsy verified dysentery was always bacillary. It is of course possible that both findings are correct if it is assumed that bacillary dysentery showed a relative increase with the war.

The physicians agreed with each other and with the necropsy observations that the major fatal diseases were tuberculosis, dysentery and pneumonia. To these they added as important and common diseases: diarrhea and gastroenteritis, hookworms and ascariasis, nephritis, epidemic conjunctivitis, scabies and occasionally epidemic colds, dengue and influenza.

They further agreed that the degenerative and retrogressive diseases were uncommon, rare or absent. Arteriosclerosis was characterized as uncommon, as was hypertension. Both were thought to be more common in the cities, in old men, and sake drinking was thought by some to be an etiologic factor—a point of interest to those who believe that alcohol relaxes the arteries. Angina pectoris and coronary occlusion were said to be rare, but cerebral apoplexy was thought to be fairly common in old people. Cardiac failure and heart disease of all types were uncommon. Many people were said to reach 80 years of age, and a few lived to 100.

Cancers were said to be fairly common in old people. Their incidence was generally given in the following order: gastric, uterine, mammary, esophageal and lingual. The larynx, the penis and the liver were each mentioned only once as a site of cancer. Sarcoma was said to occur rarely and then only in bones and in the vagina. Leukemia had never been seen by most of these physicians.

Special attention was given to the infectious diseases, and some interesting answers were recorded. The following diseases were said not to occur on Okinawa: anthrax, botulism, glanders, schistosomiasis, typhus and yaws. Cholera formerly caused epidemics but had not been seen for over forty years. Plague was introduced once long ago into Naha, the principal seaport and capital, but was promptly stopped by quarantine. Smallpox was no longer present because every child was repeatedly vaccinated. Tsutsugamushi was said to be no nearer than Formosa.

Diseases described as rare included the following: poliomyelitis, which is seen occasionally in the summer; scarlet fever, although they saw this disease commonly in Tokyo and elsewhere as medical students; rabies, which was present only rarely and then in Naha, the only place on the island where dogs were kept; rheumatic fever, the low incidence of which corresponds with that of scarlet fever. However, the incidence of rheumatic fever is probably not as low as these physicians believed, for endocarditis of rheumatic type was found in 4 hearts at necropsy.

Diseases described as uncommon included: mumps, which many children were said to escape; bacterial endocarditis; diphtheria, which was found at all times of the year, the island being subtropical; meningitis, which was usually tuberculous and found chiefly in children; septicemia. Malaria was said to be formerly contracted only on the north end of Okinawa and on some of the adjacent islands. Syphilis was seen practically only in young men who had been with prostitutes in cities (Naha). Both chancres and gummas had been recognized, the latter on the legs and in the liver. Gonorrhea was commoner than syphilis, and it occurred under similar conditions.

Diseases said to be common included the following: tuberculosis, which was most common in young adults of both sexes but occurred occasionally in younger or older persons. Several doctors volunteered the information that it was especially common in the young people who had worked in the big industrial cities of Japan, such as Osaka. Diarrhea was said to be common, especially in the summer. A small percentage of the patients had amebic dysentery, which was often fatal in infants and very aged persons. Bacillary dysentery, the physicians said, was rarely found in Okinawans. Measles and whooping cough were mild diseases that occurred in epidemics nearly every summer and autumn, and sooner or later every person was attacked. Pneumonia occurred commonly in all months and at all ages but especially in children under 10 years old, in whom it was often fatal. Tetanus was seen in farmers as a consequence of injuries and in newborn infants as a fatal infection of the umbilical cord. (Childbirth was usually attended by relatives or friends, less commonly by a midwife, and by a physician only in case of complications.) Ascaris and ankylostomiasis were described as common. The latter was said to be an infection predominantly of farmers. Sometimes it produced anemia in children. Infection by Taenia saginata was distinctly less common, and trichinosis was rare. Filarial infection was common, but elephantiasis was not a big problem. It occurred mainly on the southern and eastern end of Okinawa and on some of the outlying small islands. Scabies was a common infection of children before the war, but the widespread, heavy infestations with lice seen after the invasion and during these necropsies were a product of the war.

Certain diseases were placed in a special group because they occurred in epidemics at irregular intervals as follows: Dengue occurred at irregular intervals during the summer and was rarely fatal. Typhoid occurred irregularly in the summer, and the mortality was high. Encephalitis, believed to be Japanese encephalitis B, was a serious disease which occurred in small epidemics during the summer months at irregular intervals of a few years. Epidemic conjunctivitis occurred nearly every summer and every autumn in all age groups but predominantly in children. There were about a thousand lepers collected in a government leprosarium on a small outlying island. The incidence of this disease was stated to be decreasing.

It was the opinion of these physicians that there was little or no malnutrition or vitamin deficiency on the island. Anemia was present only in some cases of hookworm infection, in children. Pernicious anemia was said to be rare. Toxic goiter was rare. Diabetes mellitus was rare and was seen only in persons who were more than 40 years of age.

## COMMENT

Apart from the combat injuries these necropsies reveal differences from what would be expected in a similar series in the United States. Some diseases were commoner, a few were rarer, and the evidence with respect to others was inconclusive. The diseases which were rarer are especially intriguing, because their study offers the possibility that the etiologic factors may be discovered.

The most striking finding was the low incidence of retrogressive and degenerative changes. Senility came late, and cardiac and skeletal muscles remained well preserved even in the aged. Arteriosclerosis also developed late and to a moderate degree or not at all, and its lethal sequels in the brain, the kidneys and the heart were never seen. Hypertensive cardiovascular-renal disease was not seen except for 1 case of the type associated with toxemia of pregnancy. In fact, heart disease of all types, including congenital, rheumatic, bacterial endocarditic, syphilitic, hypertensive and coronary arteriosclerotic, was uncommon or absent. Renal diseases of all types was rare. Although cirrhosis of the liver was common, disease of the biliary tracts, including cholelithiasis, was not. After the life of these people had been studied, two possible etiologic factors appeared outstanding in explanation of these observations. They were: (1) a low tension, placid, although physically strenuous, life and (2) a simple, predominantly vegetarian diet.

The low incidence of malignant neoplasms, although expected, was also of interest. The explanation might lie in the relative absence of factors sometimes considered to be etiologically important. For example, stasis of ducts and cystic disease were not found in the mammary gland,

and the history of these women was typically one of numerous pregnancies with prolonged periods of lactation. The mammary glands of women past the teens appeared small and pendulous, but the glandular tissue was abundant and remained remarkably well preserved. These women rarely had erosions or infections of the uterine cervix. There was a suggestion of excellent endocrine balance in the absence or the low incidence of hirsutism in women, pathologic obesity, thyroid disease, diabetes, cystic diseases of the mammary gland, fibroids and endometrial disease of the uterus, and nodular hyperplasia of the prostate and the adrenal glands. Vitamin deficiencies with metaplasias in various epitheliums were probably absent. With respect to the alimentary tract, the diet was simple, bulky and predominantly vegetarian. There was no disease of the stomach except ulcers; these were acute and may have been related to the psychosomatic stress incidental to the bombing and invasion. There were no scars of healed peptic ulcers. Bowel habits are said to be excellent, testified to also by the absence of pseudodiverticula of the colon. There were few polyps of the colon, and appendical disease was rare. The skin was deeply pigmented against the tropical sun, and there were no industrial hazards, as possible explanations for the absence of cancers of the skin and of the respiratory tract. Lithiasis of any location was uncommon.

Endocrinologically, these people appeared to be remarkably well balanced. They were highly fertile. Disease of the thyroid, parathyroid, pituitary and adrenal glands, the pancreas and the gonads was either nonexistent, rare or unrecognized. The uteri rarely had fibroids, and the prostates equally rarely showed benign adenomatous hyperplasia. There was no instance of pathologic obesity and no hirsutism in women. The thyroid glands were small and without nodules or adenomas; only 2 contained colloid cysts. These people had no acne vulgaris.

The most important medical problems apart from the combat injuries were the infectious diseases. Tuberculosis, dysentery, pneumonia and tetanus took heavy tolls. Filariasis appeared to be common but was of a benign form which led to little elephantiasis. The incidence of intestinal helminthic infections was high but here again the clinical effects were negligible. Many other diseases present in tropical countries and expected on Okinawa were absent.

Benjamin recently reported on a series of necropsies comparable to that presented in this paper. Except for a lower incidence of tetanus in his series, the results are in close agreement.

# BILATERAL OVARIAN APLASIA

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BILATERAL aplasia of the ovaries unassociated with gross congenital malformation allows an opportunity for a study of the part played by ovarian function in the development of the human female. Kermauner [1] in 1912 critically reviewed the literature and considered most of the reported cases to be of doubtful validity because of lack of detailed histologic examination. Since then 6 well authenticated cases in which the autopsy reports approach completeness have been recorded by Pich,[2] Rössle and Wallart,[3] Graber,[4] Olivet [5] and Schürmann.[6] To these Pich would add the rather more doubtful case of Randerath,[7] though histologic examination was incomplete, and that of Priesel,[8] in which pathologic destruction of the ovaries could not be excluded.

That this interesting and fundamental deficiency is not confined to the human subject but can be found throughout the whole vertebrate phylum is evidenced by the reports of its having occurred in fish and other animals (Kermauner [1]), in the reptile Lacerta (Jacquet [9]), in the pigeon (Riddle [10]) and in the female rat (Beach [11]).

The reported cases of aplasia of the ovaries of the human subject have many characteristics in common. The subject is recognizably female but shows no secondary sexual development; primary amenorrhea is present and underdevelopment of the external and the internal genitalia is found. In several of the cases the subject has been below

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the average height, and the term "sexogenic dwarfism" has been used in this connection by Rössle and Wallart.[8] Coincidental minor congenital abnormalities are frequent.

One other case is now recorded, compared with the other reported cases and discussed in the light of modern theories of sex determination and development.

## REPORT OF A CASE

A white unmarried woman aged 35 years was admitted, April 6, 1944, under the care of Dr. T. H. Boon. She complained of painful swelling of the left leg and buttock of seven days' duration. Previously she had always been pale and thin and had never menstruated. Twelve months earlier she suffered from a "nervous breakdown" which lasted a few weeks. Three months before admission the last symptoms recurred and in the ensuing two months she lost 10 Kg. On admission she showed an edematous, reddened left leg and a swollen doughy abdomen. There was complete absence of secondary sexual characteristics, the blood pressure was 130 systolic and 90 diastolic, and the urine revealed a trace of albumin.

Roentgen examination of the lungs, April 11, showed an opacity of the left middle zone suggestive of tuberculosis. (A previous examination, February 11, had shown no abnormality.) The radiologist also reported that the sella turcica was small. The red blood cells numbered 3,200,000 per cubic millimeter, and the hemoglobin content was 54 per cent (Sahli). The clinical diagnosis was abdominal and pulmonary tuberculosis and questionable Simmonds' disease. Estimation of 17-ketosteroid excretion was planned, but the patient died April 12, before this could be carried out.

*Autopsy* (April 14).—The length of body from vertex to heel was 165 cm. The distance between the anterior superior iliac spines was 22.5 cm. No pubic nor axillary hair was present, and the vulva showed only scanty hair. The hair of the head and the eyebrows appeared normal. The breasts were not developed beyond the infantile stage. The skeletal development appeared normal, and all the epiphyses were closed.

There was moderately active caseous tuberculous lymphadenitis affecting the cervical, mediastinal, portal, mesenteric and para-aortic lymph nodes. A chronic tuberculous ulcer of the ascending colon had been causing chronic obstruction, and there was recent tuberculous peritonitis. The tuberculous process had caused thickening of the broad ligaments which partially obscured the uterine tubes. Recent tuberculous lesions were present in the lower portion of the upper lobe of the left lung. Culture showed the tubercle bacilli to be of the human type.

The kidneys were unequal in size, the right weighing 126 Gm. and the left 54 Gm. The right kidney, renal artery and ureter were normal in appearance. The left kidney showed a slightly granular surface, and the width of the cortex was reduced to 0.2 cm. The left renal artery bifurcated 1.5 cm. from its origin and was not reduced in size. The left ureter was normal in size.

The external genitalia were definitely female but were not developed beyond the prepubertal stage. The vaginal introitus was small and the wall smooth. The uterus was infantile with a circular external os. The cervix measured 2.5 cm. and the body 2.3 cm. in length, the ratio lying between that of the infantile and that of the adult uterus. Both uterine tubes were recognized; they appeared thin and underdeveloped. No ovaries were discovered, and no ovarian tissue was found in the usual ectopic sites.

An antemortem thrombus was present in the left iliac vein, the left uterine plexus and the left femoral vein. There was no pulmonary embolism.

The aorta had a maximum circumference of 4.5 cm., and the wall appeared thin; there was no coarctation. The main blood vessels showed no abnormality.

The endocrine glands were grossly normal and will be described later with their histologic appearances.

The other organs showed no obvious abnormality, and there were no other developmental errors.

*Histologic Examination.*—Uterine Tubes: Serial blocks for histologic examination were cut along the whole length of each uterine tube at right angles to the long axis. Sections from these showed that each tube was the site of recent tuberculosis, which had nowhere destroyed the structure of the organ. The surrounding tissues showed many foci of tuberculosis with formation of giant cell systems, but everywhere the tuberculous lesion was of recent origin. There was no evidence of older tuberculosis or of other pathologic processes which might have destroyed the ovaries.

In the distal third of each mesosalpinx was found a collection of tubules which on first sight resembled epididymis (fig. 1). These tubules were lined by an epithelium which varied from a low cubical to a high columnar type, with occasional ciliated cells. A few of the cells contained acidophilic granules, and the lumens of several of the tubules contained amorphous acidophilic material. One lining cell was seen in mitosis. Several of the tubules appeared to be dilated, and one or two were definitely cystic. Scanty smooth muscle fibers arranged concentrically could be made out in the walls of most of the tubules, but in several tubules muscle appeared to be absent. The tubules were arranged in loose coils in a delicate collagenous tissue. Most of these tubules were similar to the epoophoron found in this position throughout life. The epoophoron of the present subject has been compared with those of 6 women in the same age group who had undergone hysterectomy, and though more muscle is present in some of the control specimens, no essential structural difference has been found (fig. 2; this control section shows the greatest difference observed). A hydatid of Morgagni was present showing no unusual characteristics. The duct of Gartner was not found.

Sections from one block showed in a dense collagenous stroma a collection of large cells with abundant acidophilic granular cytoplasm and round, slightly eccentric, deeply staining nuclei (fig. 3). Some of these cells contained a few fine golden brown granules which were negative for the prussian blue reaction and resembled the pigment of brown atrophy. These cells were not in close relation to the epoophoron; they were indistinguishable from interstitial cells and were regarded as such.

No ovarian tissue, cortical or medullary, was found in any of the blocks of tissue.

Uterus: The endometrium was thin and showed no evidence of estrogenic stimulation. The endometrial and cervical glands appeared scanty and underdeveloped.

Vagina: The epithelium was thin, consisting only of three to four layers of squamous epithelial cells (fig. 4). No glycogen was demonstrated, but in view of the interval of time between death and autopsy this may be of little significance.

Breast: A hemisection of the organ taken through the nipple (fig. 5) showed only a few underdeveloped ducts, the mouths of which were plugged with keratinized cells. No acini were noted. A considerable amount of muscle was to be seen in the nipple, but the latter hardly projected above the surrounding skin. The total thickness of breast tissue was less than 1.0 cm.

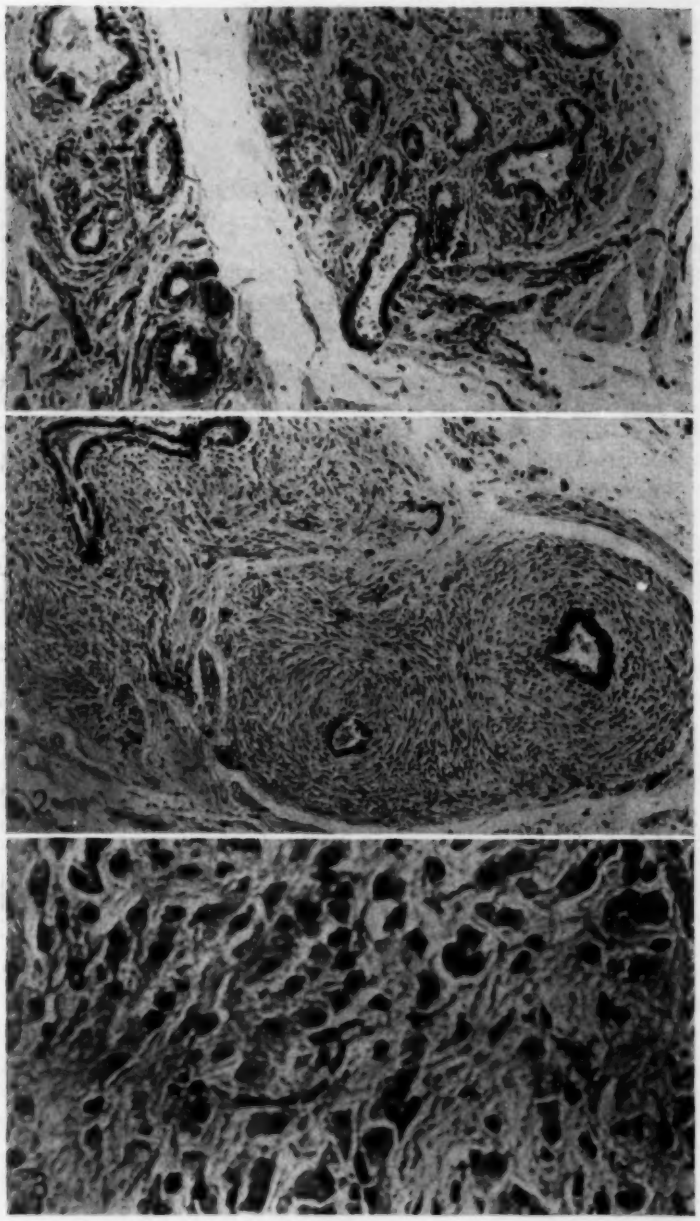

Fig. 1.—Epoophoron showing structure of tubules found in the mesosalpinx. Hematoxylin and eosin; × 92.

Fig. 2.—Epoophoron from a woman aged 45 for comparison with that in figure 1. Hematoxylin and eosin; × 92.

Fig. 3.—Section showing interstitial cells in collagenous stroma. Hematoxylin and eosin; × 480.

Adrenal Glands: The combined weight was 12 Gm., and as the usual weight found with a comparable amount of dissection is in the region of 16 Gm., the glands must be considered small. Histologically they show no obvious abnormality.

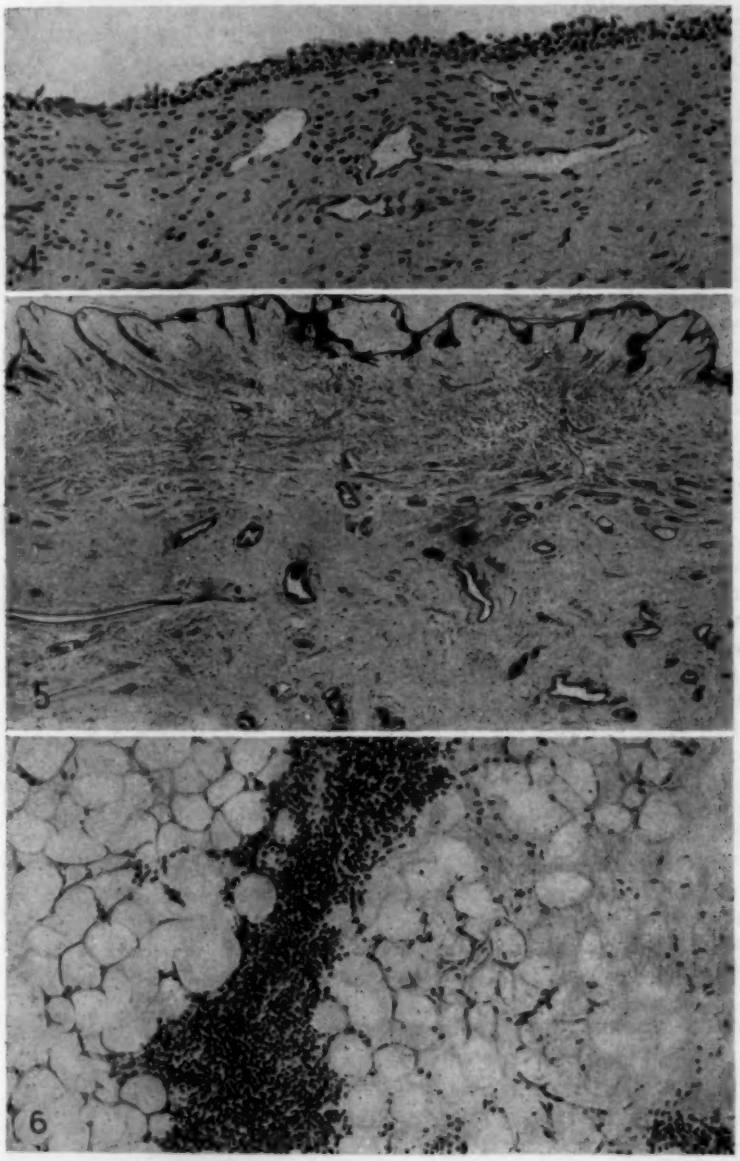


Fig. 4.—Section of vaginal wall showing thinness of the epithelial lining. Hematoxylin and eosin; × 170.

Fig. 5.—Section of breast cut through the nipple showing the entire thickness of the organ. Hematoxylin and eosin; × 16.

Fig. 6.—Thymus showing the marked degree of physiologic involution. Hematoxylin and eosin; × 130.

Pancreas: This was normal in size and histologically the exocrine and endocrine tissue appeared normal.

Thyroid Gland (12 Gm.): The gland was definitely small, but small glands are often found in patients who have had a prolonged wasting illness; so this finding is probably not significant. Microscopically the vesicles were of moderate size, lined by a low cubical epithelium and filled with acidophilic resting colloid. Much brown atrophy pigment was found in the epithelium.

Thymus: This showed marked adiposity and floated in water. Microscopically, only a few strands of thymic tissue were found lying in adipose tissue; they consisted of medulla without cortex, and there were only scanty and degenerate Hassall's corpuscles. There was no interlobular fibrosis, and the condition was one of physiologic involution (fig. 6).

Pineal Gland: This measured 1 by 0.5 by 0.3 cm. and showed a central cystic space 0.1 cm. in diameter. Microscopically the cells showed small pyknotic nuclei and contained much brown atrophy pigment. A moderate amount of calcification was present.

Pituitary Gland: The gland measured 1.6 by 1.2 by 0.8 cm. and was within the normal limits of size. Horizontal sections were made at various levels and stained with a modified Mallory's connective tissue stain (McFarlane[12]; McLetchie[13]) and a differential count was carried out according to the method of Rasmussen.[14] This showed 48 per cent chromophobes, 44 per cent eosinophils and 8 per cent basophils, which is within normal limits.[15] There was a moderate amount of basophilic infiltration of the posterior lobe, which showed a considerable amount of brown, prussian blue–negative pigment. The basophils of the anterior lobe were well granulated and showed in some cases a moderate amount of fine vacuolation of a nonspecific type. No hyaline change was found in the cytoplasm of the basophils, and the relative size ratio of the eosinophils and the basophils was maintained. The eosinophils were normally granular and showed no evident abnormality.

Right Kidney: Scanty, scarred glomeruli were found, and many calcified casts were seen in the tubules.

Left Kidney: This showed almost complete atrophy, only a few unscarred glomeruli being recognized. The tubules were dilated and filled with acidophilic colloid-like material; they showed no calcified casts. There was marked intertubular fibrosis of the medulla, which was infiltrated with lymphocytes and plasmocytes.

Whether the lesion of the left kidney was due wholly to previous pyelonephritis or was due in part to hypoplasia is difficult if not impossible to decide, but the presence of plasmocytes, the normality of the artery and the ureter and the fact that the lesions correspond with no known developmental defect are in favor of an acquired lesion.

## PATHOLOGIC FEATURES IN PRESENT CASE AND PREVIOUSLY RECORDED CASES OF OVARIAN APLASIA COMPARED

Apart from variations in minor details the findings in all the recorded cases of ovarian aplasia show a close similarity. Detailed descriptions are available

12. McFarlane, D.: Stain Technol. **19**:29, 1944.
13. McLetchie, N. G. B.: J. Endocrinol. **3**:323, 1944.
14. Rasmussen, A. T.: Am. J. Path. **5**:263, 1929.
15. Rasmussen, A. T.: Am. J. Path. **9**:459, 1933.

in the literature,[16] and only a summary of the main features will be given under the following headings.

*Ovarian Tissue.*—This has been absent from the usual position, and none has been found in ectopic sites; there has been complete absence of sex cells and primordial follicles. Connective tissue thickenings have been described as occurring in the expected position of the ovary in several cases and in some of them pseudoglomerular structures were found. In the present case no such thickenings were recognized but, if present, might well have been obscured by the tuberculous process.

*Müllerian Derivatives.*—In adults the internal genitalia have been underdeveloped and might justifiably be called infantile. In the case of Graber,[4] that of a 9 week old infant, it is noteworthy that except for the lack of ovaries and slight uterus bicornis arcuatus the genital apparatus was normal in development according to the age.

*Wolffian Derivatives.*—The condition of the structures found in the mesosalpinx and the mesovarium has varied. In the infant described by Graber[4] the paroophoron was noted as being unusually strongly developed, while in the first case of Pich,[2] that of an 18 year old girl, a collection of canaliculi resembling underdeveloped epididymis corresponded to the paroophoron. The latter was said by Graber to be rarely found in normal females after 5 years of age.

The epoophoron, which is normally present throughout female life, was said to be absent in the second case of Pich,[2] while Schürmann[6] observed that this structure was large enough to form a visible swelling on the serosa, and Rössle and Wallart[3] noted a marked epoophoron partially cystadenomatous in character. Olivet[5] did not find any enlargement of this wolffian remnant.

Interstitial cells and tissue resembling the rete ovarii were noted by Rössle and Wallart[3] and by Pich.[2] Graber[4] stated that interstitial cells were absent, while in the reports of other cases cells of this type were not specifically mentioned.

In the present case no paroophoron was found; the tubules of the epoophoron were numerous and in appearance resembled the structure of an epidydimis. Interstitial cells were present, embedded in a connective tissue stroma.

*Other Endocrine Organs.*—There have been no constant abnormal findings in the other endocrine organs. The pituitary gland has been variously reported as showing eosinophilia[17] or basophilia,[2] but in the absence of a differential count arrived at by a standard method[14] little significance can be attached to such observations.[15] In the present case no abnormality was noted in the pituitary gland. The thymus in the case now reported showed marked physiologic involution, and similar findings were reported by Pich.[2]

*Skeletal Development.*—Retardation of skeletal development has been noted, many of the subjects being below average height and showing late closure of the epiphyses.

In the present case, the height was within the average range, and the epiphyses were closed.

*Secondary Sex Characteristics.*—Except for the variable presence of pubic and axillary hair, the secondary sex characteristics have been absent in adults. Wilkins and Fleischmann[18] pointed out that the presence of pubic and axillary

16. Pich.[2] Rössle and Wallart.[3] Graber.[4]

17. Rössle and Wallart.[3] Graber.[4] Olivet.[5] Randerath.[7]

18. Wilkins, L., and Fleischmann, W. F.: J. Clin. Endocrinol. 4:357, 1944.

hair is of importance when one is differenting aplasia of the ovaries from panhypopituitarism, in which sexual hair is uniformly absent.

*Coincidental Minor Congenital Abnormalities.*—While none were present in the case reported here, with the possible exception of the sclerosed left kidney, conditions, such as horseshoe kidney, cervical ribs, fusion of ribs, neurofibromatosis and thinning of the aortic wall have been found.

## COMMENT

It has recently been shown by Everett [19] that in the mouse the primordial germ cells are originally present in the gut endoderm and later migrate to the genital ridge epithelium. If the genital ridge tissue be transplanted inside the capsule of the kidney of a litter mate of the mother of the donor after the primordial germ cells have reached it, a typical ovary or testis develops but if it is transplanted before they do so, no sex cells will be formed in the genital ridge tissue although the associated genitourinary ducts will develop.

Graber [4] stated that the primordial sex cells are responsible for the formation of the ovary as a whole, and Wilkins and Fleischmann [18] arrived at a similar conclusion from a study of a series of clinical cases in which biopsies had been performed. By ablation experiments Reagan [20] and others showed that in the absence of primordial sex cells connective tissue thickenings may be found in place of the ovaries. Graber [4] regarded the connective tissue bodies in his case as mesonephric remains because of the presence of regressing pseudoglomerular structures, while Wilkins and Fleischmann [18] explained the position of the connective tissue bodies in their cases as being due to the carrying forward of the primitive genital ridge tissue by the mesentery which forms the broad ligament. It may be noted that in absolute size these bodies are much larger than the original genital ridges, and this may be due to continued growth of this tissue in which the proliferation of an ovarian cortex has not taken place. In the absence of evidence of pathologic destruction of the ovaries either in utero or after birth it seems reasonable to assume that the connective tissue bodies may represent the genital ridge tissue on which the primordial sex cells have failed to induce an ovarian cortex.

That bilateral absence of the ovaries is not produced by bilateral occurrence of the conditions which lead to the more common unilateral defect is shown by the fact that the latter is associated with partial or complete deficiency of the ipsilateral Müllerian duct [21] and is also frequently associated with renal agenesia on the same side. This seems to suggest that in the cases of unilateral defect there is a failure

19. Everett, N. B.: J. Exper. Zool. **92**:49, 1943.

20. Reagan, F. P.: Anat. Rec. **11**:489, 1916.

21. Shumacker, H. B.: Arch. Surg. **37**:586, 1938. Varino, G. A., and Beecham, W. D.: Am. J. Obst. & Gynec. **41**:124, 1941.

of normal development of the genital ridge tissue as such, while in the cases of bilateral defect it is only that portion which requires the presence of the primordial germ cells that fails to develop normally.

The more commonly accepted theory of sex determination and differentiation is that the genic balance of the parent germ cell decides the sex and whether an ovary or a testis is to be formed from the undifferentiated gonad. The differentiated gonads then elaborate embryonic sex hormones which guide the development of the genital apparatus. On the other hand, the occurrence of bilateral ovarian aplasia in subjects in which the sex ducts are developed to an infantile stage would appear to support, as far as the female is concerned, the view put forward by Moore,[22] that the characters of both the gonad and the sex duct system are genetically determined. In connection with the possible effect of maternal hormones, Wilkins and Fleischmann [18] remarked that this cannot be entirely excluded but that it is difficult to concede the influence of maternal hormones on sex determination unless one grants also that the embryonic testis produces hormones capable of reversing the action of maternal estrogens. That this is not so is evidenced by the first case reported by Altmann [23] of congenital absence of the testes.

It is generally accepted that the presence of normally functioning ovarian tissue is necessary in the female to bring the genitalia to full maturity and to bring about the appearance of the secondary sex characteristics. No departure from this view is necessitated by the findings in these cases of bilateral ovarian aplasia.

Regarding the wolffian remnants, these show great variation in normal subjects, but if one accepts the findings in the few reported cases as a definite though variable hypertrophy, some explanation must be sought. Graber [4] expressed the belief that ovarian hormones control the regression of the wolffian remnants and that any enlargement might be explained as being due to an inherent growth tendency of the latter in the absence of ovarian inhibition. Recently Burrows [24] has stated that the inhibitory action of estrogen on the wolffian system is slight and inconstant. Ramsay and McCahey [25] pointed out that there is a correlation between the amount of rete tissue and associated interstitial cells and the amount of wolffian remains, and that where the former are abundant the latter are also prominent. It is therefore possible that the interstitial cells may produce a secretion which causes growth or inhibits the retrogression of the wolffian remnants. One case has been

22. Moore, C. R.: Am. Naturalist **78**:97, 1944.

23. Altmann, F.: Virchows Arch. f. path. Anat. **276**:455, 1930.

24. Burrows, H.: Biological Actions of the Sex Hormones, London, Cambridge University Press, 1946.

25. Ramsay, A. J., and McCahey, J. F.: Am. J. Obst. & Gynec. **36**:104, 1938.

reported in which enlarged paraurethral ducts were found,[2] but the finding is of doubtful significance, and there is no real evidence suggesting that the interstitial cells have had any virilizing influence on these subjects. It is possible that when a larger series of cases is available, especially if actual measurements of the wolffian remnants are made, the enlargement may be found to be within the limits of normal variation.

There is no agreement as to the cause of the skeletal immaturity and underdevelopment noted in several of the cases and also in clinical cases of ovarian hypofunction recently reported by Wilkins and Fleischmann[18] and by Albright, Smith and Fraser.[26] In the case reported here dwarfism is not shown, nor any evidence of skeletal immaturity, and this is considered to favor the view of Wilkins and Fleischmann[18] that there may be a genetic basis for this condition and that the effect of the absence of the ovary, whether it results directly or through lack of stimulation of other endocrine organs, is not at any rate wholly responsible.

## SUMMARY

Bilateral absence of the ovaries was observed in an adult female of normal stature. The genitalia, both internal and external, were developed to the infantile stage; there were no secondary sexual characteristics and primary amenorrhea was present. No other congenital anomaly was found.

The fact that this selective congenital defect repeatedly occurs in closely parallel cases, with but minor variations and with no evidence of pathologic destruction, suggests that in these cases the aplasia of the ovaries may be genetically determined.

No specific changes in the other endocrine organs attributable to the absence of the ovaries can be found.

The occurrence of bilateral ovarian aplasia supports the view that the establishment and differentiation of the specific characters of the gonad and duct system which determine the sex of the individual are largely under genetic control.

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26. Albright, F.; Smith, P. H., and Fraser, R.: Am. J. M. Sc. **204**:625, 1942.

# ECLAMPSIA

## Report of a Case in Which There Was Extensive Destruction of the Brain

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THE BRAINS of women who have died in an eclamptic attack have been examined rather frequently. In most cases only minor changes have been found. Apparently, few patients surviving eclampsia show late sequelae. Except in the report by Lowenberg and Lossman,[1] there is no description of the brain of a patient who has survived eclampsia for an essential period, after development of severe neuropsychiatric symptoms as a result of the acute attack. Lowenberg and Lossman examined the brain of a woman who had eclampsia and subsequently showed symptoms of severe neurologic disturbance and progressive mental deterioration. She died seven years later. Her brain was atrophic; the cerebral cortex had undergone widespread degeneration, and the centrum semiovale was demyelinated.

Our report describes another brain of this type not only because the condition is rare but because the changes in the brain are those of a patient who survived for only three months after the eclamptic seizures.

### REPORT OF CASE

A white girl aged 15 years entered the regular obstetric service at St. Luke's Hospital, Chicago, Jan. 9, 1945, with the diagnosis of preeclamptic toxemia. When admitted to the prenatal clinic, Sept. 15, 1944, she was about five months pregnant. An uneventful course followed until Dec. 15, 1944, when marked edema of the ankles was observed, and her blood pressure, which had been 105 mm. of mercury systolic and 80 mm. diastolic, had risen to 118 mm. and 88 mm., respectively. During the following weeks the edema persisted and the blood pressure remained slightly elevated. When admitted on January 9, the patient had a blood pressure of 130 mm. systolic and 108 mm. diastolic. There was edema of the ankles. The temperature and the pulse rate were not elevated. The pregnancy seemed to be at about eight and a half months. The total nonprotein nitrogen of the blood was 22.6 mg. per hundred cubic centimeters. The urine contained 20 mg. of albumin per hundred cubic centimeters, but no casts or cells. The blood had 3,440,000 erythrocytes per cubic millimeter and 10 Gm. of hemoglobin per hundred cubic centimeters. With rest in bed, the blood pressure remained about 130 mm. of

From the Henry Baird Favill Laboratory of St. Luke's Hospital and the Department of Pathology of the Chicago State Hospital.

1. Lowenberg, K., and Lossman, R. T.: Am. J. Path. **19**:697, 1943.

mercury systolic and 110 mm. diastolic. On January 12 labor was induced medically with castor oil. During labor the patient had five generalized convulsions. After delivery she had a series of almost continuous convulsions for about forty-five minutes, which were terminated by an intravenous injection of sodium amytal. During these convulsions she became dyspneic and markedly cyanotic. Toward the end of the series the blood pressure dropped to 60 mm. systolic and 0 diastolic. Oxygen was given. However, the patient never regained mental consciousness. She lived on for about three months, leading a vegetative form of existence, and was fed by stomach tube. During several weeks following delivery she occasionally had convulsions, which were controlled with sodium amytal. Shortly after the series of convulsions following delivery the spinal fluid was clear, under normal pressure, contained 20 cells per cubic millimeter and had 150 mg. of protein per hundred cubic centimeters. No abnormalities were demonstrated by neurologic examinations until January 23, when generalized spasticity was observed, and this persisted until death. Following delivery, her temperature ranged between 101 and 105 F., and on January 18 the urine contained 200 mg. of albumin per hundred cubic centimeters, many red blood cells and granular casts. The nonprotein nitrogen of the blood was 32 mg. per hundred cubic centimeters. The urine became normal, and several determinations of the plasma proteins of the blood gave values within the normal range. The patient's temperature continued to fluctuate between 101 and 104 F., and the pressure of the spinal fluid gradually increased to 210 mm. of water, February 23, but the fluid was clear. A ventriculogram, February 28, demonstrated an atrophic cerebrum and dilated ventricles. The patient continued in a vegetative state and died April 14, three months and two days after the onset of her attacks of convulsions.

*Postmortem Examination.*—The essentials of the anatomic diagnosis following complete postmortem examination were: marked encephalomalacia and atrophy of the cortex of the brain; acute purulent tracheitis and bronchitis; atelectasis of the lower lobes of both lungs; cloudy swelling and marked fatty changes of the liver; cloudy swelling of the myocardium and the kidneys; old surgical ventriculographic defect of the left parietal bone and scar of the scalp.

The symmetrically developed body of this young white woman weighed 101 pounds (45.5 Kg.) and was 161 cm. long. The heart weighed 320 Gm., and there were no significant changes of the valves or of the myocardium. The edematous hyperemic right lung weighed 390 Gm.; the left, 350 Gm. Each kidney weighed 160 Gm. The ratio of cortex to medulla and the cortical markings were not unusual. The kidneys showed moderate cloudy swelling. The pancreas had no unusual changes; it weighed 135 Gm. The spleen weighed 230 Gm., and surfaces made by cutting had a dark red pulp with small gray nodules of lymphoid tissue. The liver weighed 1,650 Gm. The lower margins were rounded, the capsule was smooth and the tissues beneath were mottled tan-brown and red-brown. Orange-yellow regions of fatty changes, 1 to 3 mm. in diameter, were scattered widely. Surfaces made by cutting had mottlings as mentioned, scattered foci of fatty changes and cloudy swelling.

The brain with the upper half of the dura (approximately 20 Gm.) weighed 990 Gm. The spinal fluid was abundant, clear and colorless. The pia-arachnoid at the base of the brain was thin and transparent. The arteries at the base had thin walls. The tissues of the cerebellum, the pons and the brain stem were firm, but those of both cerebral hemispheres, especially of the frontal, temporal and parietal regions, were soft; the convolutions were atrophic and flattened and the sulci narrowed. In the posterior portions of the parietal and the occipital lobes

the convolutions were rounded and the sulci wider. There were no unusual changes in the accessory sinuses of the cranium or in those of the dura. The examination of the cervical structures and of the right knee revealed no significant changes.

After formaldehyde fixation there were no abnormal adhesions between the dura and the brain. A small subdural hematoma, 5 by 5 cm., was present in the region of the wound resulting from the needle puncture made in the posterior portion of the left parietal lobe in taking a ventriculogram. The configuration of the brain has been mentioned. The cerebral hemispheres were soft. In coronal sections of the cerebrum, the cortex was narrowed and generally separated from the centrum ovale by a narrow layer of loose tissue parallel to the gyral surface. The white matter was pale and friable; especially the poles of the temporal lobes seemed to be softened. The basal ganglions were normal, and the lateral ventricles were moderately dilated. The cerebellum, the pons and the brain stem showed no gross changes.

*Histologic Examination of the Brain.*—Tissues from many regions of the brain were embedded in celloidin (a concentrated preparation of pyroxylin), paraffin or gelatin. Sections were stained with toluidine blue, by Van Gieson's method, and for myelin sheaths, for neurofibrils, for mesenchymal structures with tannin silver, and for lipids.

The subdural hematoma was partially organized. In the fibroplastic tissues many phagocytes contained granular blood pigment. The pia-arachnoid generally was thickened by fibrous and fibroplastic tissues. The veins were dilated, and occasionally there were extravasations. A coronal section of the cerebral hemispheres, stained for myelin sheaths (fig. 1 *A*), disclosed marked changes of the tissues. The white matter of the parietal lobe and of the second and third temporal gyri stained poorly and was much lighter than that of the darkly stained first temporal gyrus. The cortex of the temporal and parietal lobes was narrow, and the edge bordering the white matter was more sharply defined than usual. The cortex in the temporal lobe had separated from the white matter in many places. The frontal gyri had narrow, long, stretched focal regions of demyelination, which extended parallel to the gyral margin. These were in the lower part of the cortex, or at the border between the cortex and the white matter, and were sharply outlined (fig. 1 *B*). Marked and extensive destruction of the cortex was demonstrated by sections stained with toluidine blue. This was especially marked in the anterior portions of the cerebral hemispheres but occurred also in the occipital region, where in many places the usual tissue structure remained. The tissue changes in the cortex can be arranged into two main groups. In each there was marked loss of the nerve cells and fibers. The difference between them was in the subsequent reaction. In one there was an accumulation of Hortega and gitter cells, associated with a marked growth of mesenchyma, that is, a softening with organization; in the other there was proliferation only of the glia, which had replaced the nervous parenchyma, without gitter cells or an increase of mesenchyma. These forms of reaction were not separated strictly but occurred together in many foci (figs. 2 *A* and *B*; 3 *A* and *B*; 4 *A*). They were found in many places in the deeper portions of the cortex or at the border between the cortex and the white matter. They seemed to account for the separation of the cortex and the centrum semiovale. Such softenings, however, occurred also in the outer layers of the cortex or had destroyed the entire thickness of the cortical tissues. They were small and seemed not to correspond to the distribution of an artery. In a few places with mesenchymal proliferation the cortex had undergone coagulation necrosis, the tissues being reduced to a homogeneous mass without

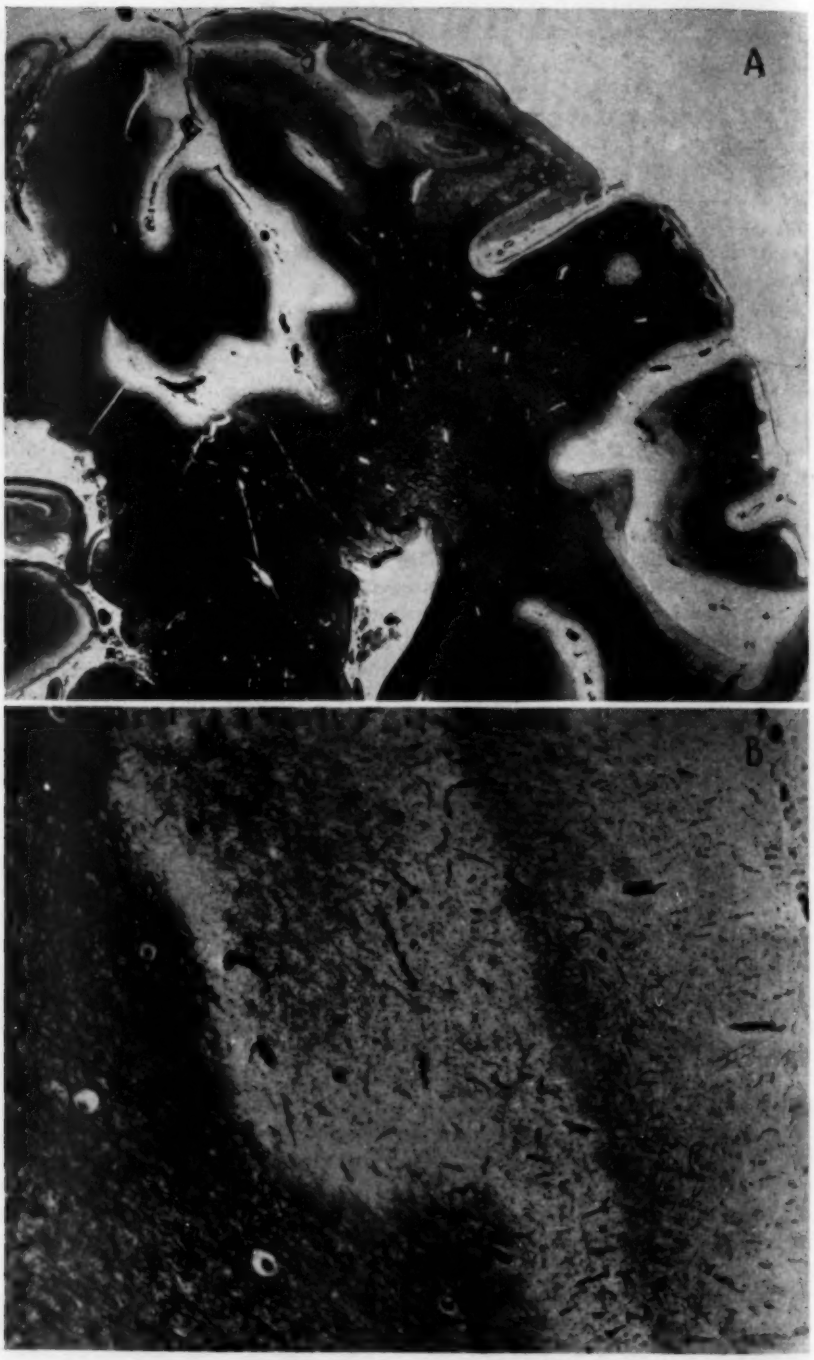


Fig. 1.—*A*, coronal section of left cerebral hemisphere. Myelin sheath staining. Note demyelination of the centrum semiovale in the frontal lobe, as well as in the second and the third temporal gyrus, and the destruction and separation of the cortex and the circumscribed foci of necrosis in the first and the second frontal gyrus.

*B*, one of the foci of necrosis. Note the sharp border, also the engorged blood vessels and hemorrhage in the center.

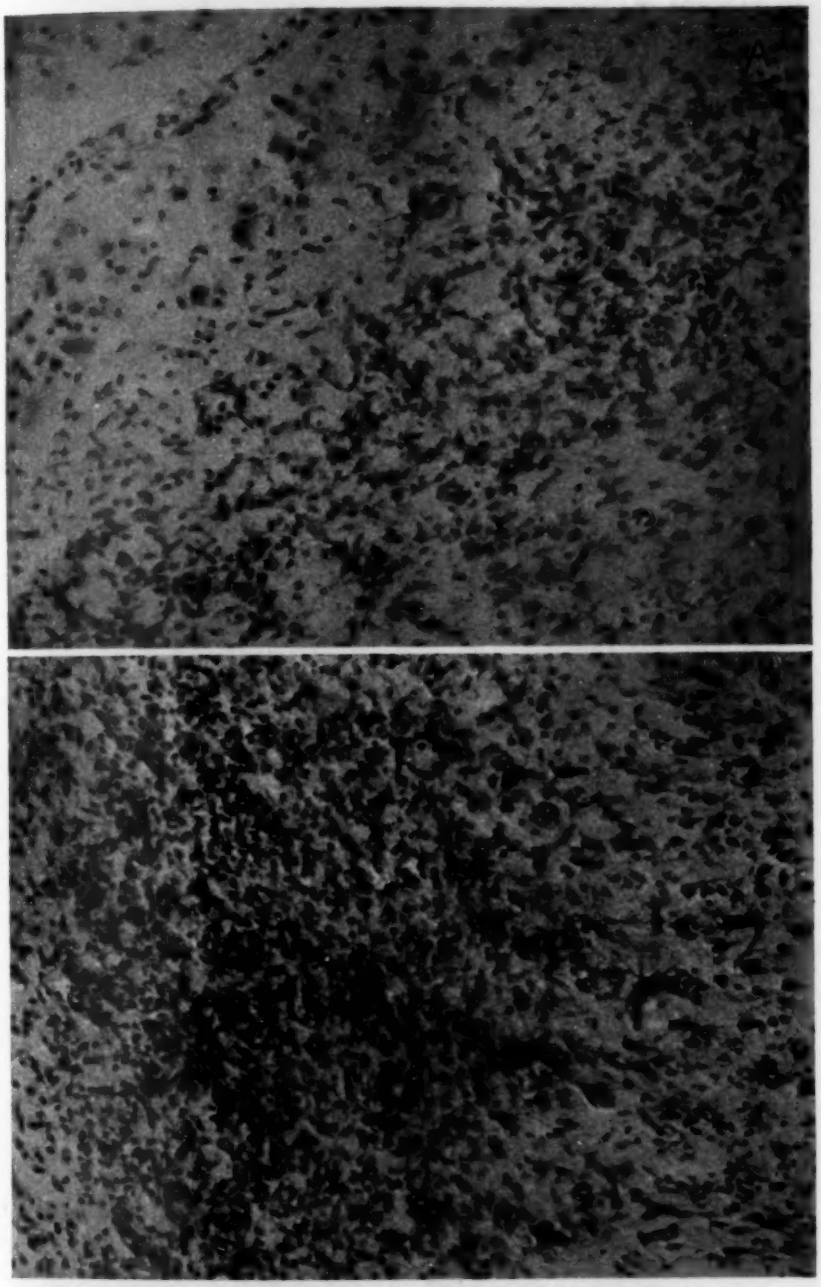

Fig. 2.—*A*, area of softening of the cortex exhibiting many gitter cells. Toluidine blue staining. Medium power enlargement.

*B*, long, stretched, narrow focus of softening in the cortex. Glia proliferation is seen in the upper layers, and newly formed vessels in laminas III and IV. Toluidine blue staining. Medium power enlargement.

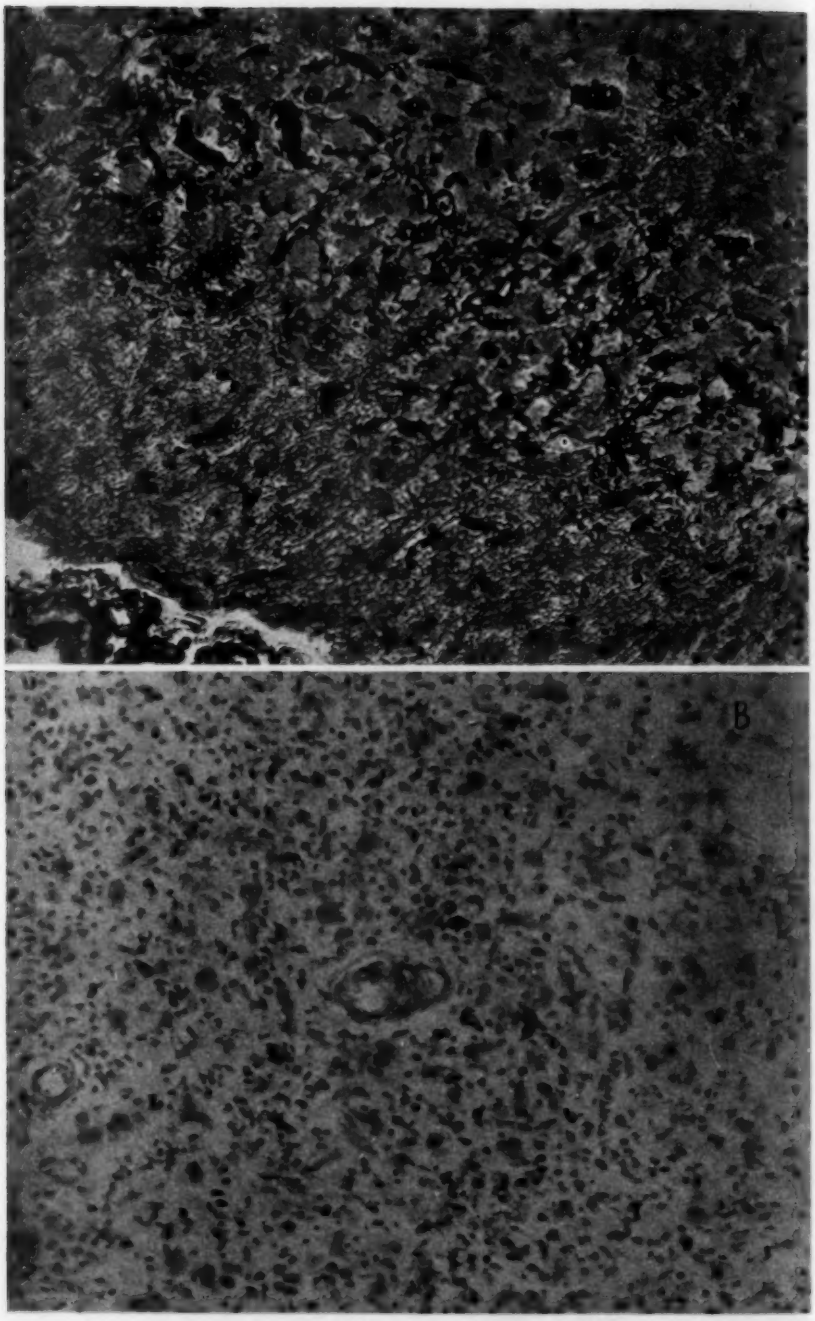


Fig. 3.—*A*, the same focus as in figure 2 *B*. Tannin silver staining to demonstrate the proliferation of the mesenchyma.

*B*, marked destruction of the cortex. Glia proliferation without reaction of the mesenchyma. Toluidine blue staining. Medium power enlargement.

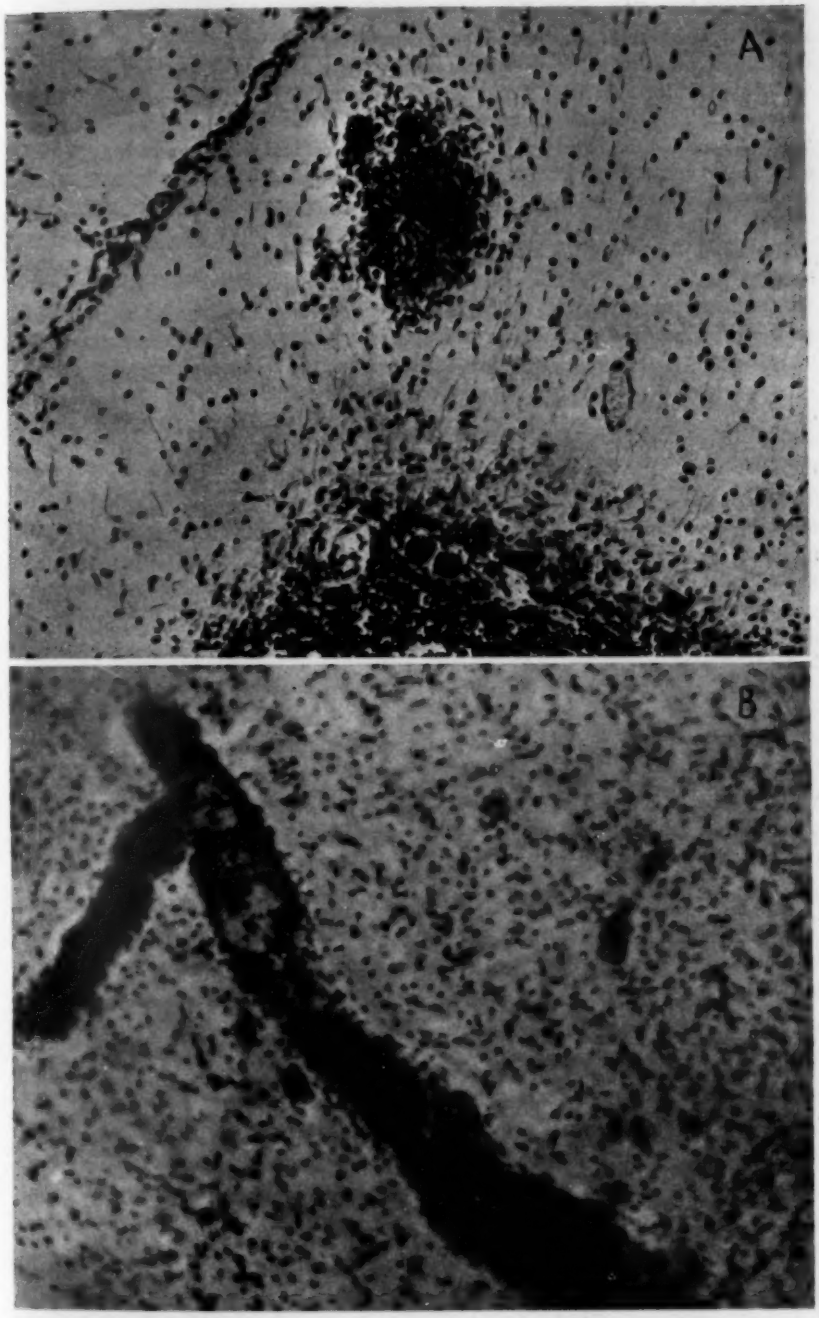


Fig. 4.—*A*, cerebellum. Focus of Hortega cells in the molecular layer. Toluidine blue staining. Medium power enlargement.

*B*, venule and capillary from the cortex. Both are engorged with tightly packed red blood cells. The venule contains a small thrombus. Van Gieson's staining. Medium power enlargement.

cells or nuclei. The capillaries and the veins of the cortex were markedly dilated, the walls being thin and formed by a single layer of endothelial cells containing fine droplets of lipid and of a few connective tissue fibrils. There were a few small platelet thrombi (fig. 4 *B*). The perivascular spaces were dilated, and occasionally small hemorrhages were observed. In the region of demyelination of the white matter the myelin sheaths had marked retrogressive changes. They were swollen or reduced to small particles and granules. The veins of the centrum ovale were dilated and had wide Virchow-Robin spaces. Sections stained with toluidine blue demonstrated proliferation of the Hortega cells and astrocytes. There were a few foci of softening in the outer capsule and around the anterior horn of the lateral ventricle.

The basal ganglions, the thalamus and the hypothalamus, the nucleus ruber, the substantia nigra and the medulla oblongata had no changes. The Purkinje cells had disappeared in large portions of the cerebellum, without reaction of the glia. Silver-stained preparations disclosed empty baskets. The cortex had small foci of Hortega cells (fig. 4 *A*). The nerve cells in the dentate nucleus were reduced markedly in number, and in the white matter there was marked proliferation of the microglia.

*Histologic Examination of Other Viscera.*—Changes were observed in the liver, the kidneys and the lungs. The liver had foci of fatty changes of the hepatic cells, but in these regions the lobular structure of the tissues was present. Elsewhere the hepatic cells and cords showed no significant changes. The capillary tufts of the renal glomeruli were cellular, had hyaline thickenings and some also a few polymorphonuclear leukocytes. The lungs had marked catarrhal bronchitis and foci of bronchopneumonia.

## COMMENT

The pathologic observations in the brain of this patient can be summarized briefly as those of a destructive process of the cortex which three months after the onset of the convulsive seizures of eclampsia was in a state of more or less advanced organization and scarification. The centrum semiovale had demyelination. The cerebellum was affected also but to a much less degree than the cerebral hemispheres. These changes are identical basically with those described by Lowenberg and Lossman [1] in their report on atrophy of the brain following eclampsia. The differences between their case and ours are essentially those dependent on the duration of the process. Lowenberg and Lossman examined a brain seven years after the eclampsia occurred; our patient died three months after the initial convulsions. Accordingly, Lowenberg and Lossman saw the final outcome of a process which we observed in a rather early, active stage. Neither Lowenberg and Lossman nor we found another report of eclampsia with similar, and as extensive, changes of the brain.

Minor injury of the central nervous system and even major damage in the form of hemorrhages have been described more frequently. Levant and Portes [2] held that hemorrhages occur in the central nervous

2. Levant and Portes, L.: Gynéc. et obst. 7:332, 1923.

system less frequently than is commonly assumed; extravasates are present in only 2.7 per cent of all cases of eclampsia. They examined 46 brains with extravasates. They observed hemorrhages in the meninges in 20, in the cerebrum and the meninges in 10 and in the cerebrum in 11. Welch [3] observed a large hemorrhage in the striatum. Wegelin [4] reported the same. Von Braunmühl [5] made a careful study of the brains of 2 women who died in the convulsions of eclampsia. In both he found diffuse damage of the nervous parenchyma and also foci of necrobiosis connected evidently with disturbances of the blood supply. He expressed the belief that vasospasms rather than venous statis had caused the damage. Sioli [6] found the same changes, that is, diffuse degeneration and focal lesions. He maintained that stasis and thrombosis of small vessels are responsible and added that in all brains examined fatty degeneration of endothelial and other cells of the vascular walls was present.

Heynemann [7] and others reported identical findings. Weiman,[8] in a résumé of the literature up to 1930, stated that in eclampsia the brain may have the signs of disturbances of the circulation with all the changes resulting from it. Diamond [9] described the brains of 5 patients, all of whom died in coma soon after the onset of eclampsia. In all, pathologic changes were present in the central nervous system. They were general or diffuse as well as focal. The diffuse pathologic changes were more marked than the focal. There were edema, degeneration of ganglion cells and reaction of the glia and of the microglia and of the meninges. Two brains disclosed inflammation, considered by the author as a form of aseptic meningitis. The focal lesions, such as small softenings, minute and massive hemorrhages and accumulations of Hortega cells, occurred less frequently than the diffuse damage.

These focal changes may represent on a small scale lesions which are identical with those we found in the form of an extensive process.

In general, the opinion of all authors seems to be that these disturbances of circulation are functional and without actual damage of the vessels. However, Winkelman [10] in a case of chorea in pregnancy found marked changes of the vessels. The vessels were narrow and

3. Welch, J. E.: Bull. Lying-in Hosp., New York **6**:12, 1909.

4. Wegelin: Berl. klin. Wchnschr. **44**:2094, 1909.

5. von Braunmühl, A.: Ztschr. f. d. ges. Neurol. u. Psychiat. **117**:698, 1928.

6. Sioli, F., in Hinselmann, H., and others: Die Eklampsie, Bonn, F. Cohen, 1924, p. 559.

7. Heynemann, T., in von Lichtenberg, A.; Voelcker, F., and Wildbolz, H.: Handbuch der Urologie, Berlin, Julius Springer, 1928, vol. 3, pt. 1, pp. 599-652.

8. Weiman, W., in Bumke, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1930, vol. 7.

9. Diamond, I. B.: Arch. Neurol. & Psychiat. **35**:1320, 1936.

10. Winkelman, N. W.: Ztschr. f. d. ges. Neurol. u. Psychiat. **102**:56, 1926.

had proliferation of the endothelial and adventitial elements. His case differed from those of the aforementioned authors insofar as his patient was sick with chorea for six months during pregnancy, in contrast with the eclamptic patients who died in acute convulsions after a short illness. Lowenberg and Lossman,[1] in discussing the genesis of the disease of their patient, assume that the initial process was necrosis of the nervous parenchyma and that it must have been caused either by functional disturbances of the circulation of the blood or by toxic influences. They decided that toxic factors acting directly on the parenchyma were responsible for the extensive damage, as a vascular factor may cause diffuse necrosis of the cortex but not of the white matter.

The histopathologic changes observed in the brain of our patient point to a vascular genesis rather than to primary degeneration of the nervous parenchyma. The small softenings found in the cortex and also in the white matter are, according to experience, definitely connected with some disturbance of the blood supply. The same reparative proliferation of the glia without involvement of the mesenchyma which was present in the cortex is a common finding in the sclerosis of the cornu ammonis in epilepsy. This sclerosis according to Spielmeyer [11] and others is due to a vascular factor. Furthermore, the enormous dilatation of capillaries and small veins is a striking feature in our case. It seems justified to assume that this vasodilation has played an important role in the genesis of the widespread focal lesions. Recently Scheinker [12] has described as vasoparalysis and vasothrombosis of the central nervous system two related conditions from which extensive and marked damage may result. The damage is vascular in origin; it is not bound to regions supplied by a small or a large artery but to those supplied and drained by capillaries and small veins. The morphologic criteria for vasoparalysis are given by Scheinker as (1) maximal distention and engorgement of the smaller veins and capillaries, (2) signs of stasis consisting in hemolysis of red blood cells, (3) degenerative changes or complete necrosis of vessel walls with increased permeability for serous fluid and red blood cells and (4) distention of the perivascular spaces, which usually contain extravasates. In venous thrombosis the wall of the vessel may appear healthy and have a well preserved endothelial lining. Adherence of the blood clot, composed of red cells, platelets and fibrin, cannot be expected, although the mere presence of clots or an amorphous mass of agglutinated red blood cells with a large accumulation of platelets and large curved strands of fibrin which fills completely the lumen of an enormously distended small venule or capillary is sufficient evidence of venous thrombosis. If these

11. Spielmeyer, W.: Arch. Neurol. & Psychiat. **23**:869, 1930.

12. Scheinker, I. M.: Arch. Neurol. & Psychiat. **52**:43, 1944; **53**:171, 1945.

changes are associated with secondary lesions of the adjacent nerve tissue that are typical of vascular occlusion and perivascular in distribution, there is little doubt that the venous occlusion ought to be regarded as thrombotic.

Our observations match the essential features of Scheinker's description. Some of the illustrations in Scheinker's report could be as well photographs taken from the brain described here. Therefore, we conclude that a vascular factor, namely, vasoparalysis, as well as venous thrombosis, is responsible for most of the lesions described. However, it is possible that a toxic factor, such as anoxemia, has caused the rather diffuse demyelination of the centrum semiovale, which in our case is less impressive than that observed in the case of Lowenberg and Lossman.

Only a brief comment is necessary concerning the relation of the clinical symptoms and the pathologic alterations in our case. The destruction of brain is extensive and intensive enough to explain the condition of decerebrate rigidity.

Finally, the question arises whether cases like that of Lowenberg and Lossman and ours are as rare as would appear from the reports in the literature. Psychotic episodes in women suffering from eclampsia are assumed to last only a short time and to terminate in complete recovery (Sioli [13]). Few reports indicate more severe and longer persisting damage. Sioli referred to 2 cases published by Westphal in 1908 and Wichura in 1912, respectively. The first author observed a psychosis after eclampsia with symptoms of aphasia, agraphia and apraxia; the patient seemed well after one year. Wichura observed a woman who two years after the onset of an eclamptic psychosis had severe organic neuropsychiatric disturbances involving memory, gnosis and praxis. However, there have been neither systematic neuropsychiatric examinations of patients who have survived eclampsia for a long time nor studies of the brains of such patients. Probably damage of the central nervous system occurs more frequently than has been reported. If destruction of nervous parenchyma is less extensive and intensive than in our case and the one described by Lowenberg and Lossman, clinical symptoms may be inconspicuous and overlooked.

SUMMARY

Eclamptic convulsions in a young woman were followed by a vegetative existence until death three months later. The brain had extensive regions of destruction in various stages of organization. The destruction was caused by vascular disturbances, especially by paralysis and thrombosis of venules and capillaries. There is only one other description of this condition in the literature.

13. Sioli, F., in Hinselmann, H., and others: Die Eklampsie, Bonn, F. Cohen, 1924.

# TEMPORAL ARTERITIS

## Report of a Case and a Comparison with Respect to Periarteritis Nodosa

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IN 1932, Horton, Magath and Brown [1] reported 2 cases of arteritis of the temporal vessels associated with fever, anorexia, malaise, anemia, loss of weight and pain in areas along the temporal arteries and over the scalp. The clinical course, ending with recovery, and the pathologic features observed in biopsy specimens did not suggest any of the known forms of arteritis, and the authors were inclined to believe that their cases represented a new clinical and pathologic entity.

Subsequent reports have added greatly to the clinical picture of temporal arteritis or, to speak more correctly, have revealed the great diversity of symptoms possible with this condition. Pain occurring in teeth,[1] ear,[2] jaw [2] and occiput [3] suggested involvement of other branches of the external carotid artery. Relatively frequent ocular symptoms,[4] occasional symptoms suggesting cerebral damage,[5] and pain of the extremities [4a] added to the possibility that this condition may be associated with widespread involvement of the arterial tree and not necessarily with local involvement of the temporal arteries only.

Gilmour [6] reported the necropsy observation in 4 cases resembling those of temporal arteritis in their symptoms. His observations revealed widespread arteritis with involvement of the aorta, the internal and the external carotid artery and the subclavian, innominate, cerebral and

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1. Horton, B. T.; Magath, T. B., and Brown, G. E.: Proc. Staff Meet., Mayo Clin. **7**:700, 1932.

2. Horton, B. T., and Magath, T. B.: Proc. Staff Meet., Mayo Clin. **12**:548, 1937.

3. Bowers, J. M.: Arch. Int. Med. **66**:384, 1940.

4. (*a*) Jennings, G. H.: Lancet **1**:424, 1938. (*b*) Scott, T., and Maxwell, E. S.: Internat. Clin. **2**:220, 1941. (*c*) Johnson, R. H.; Harley, R. D., and Horton, B. T.: Am. J. Ophth. **26**:147, 1943. (*d*) Shannon, E. W., and Solomon, J.: J. A. M. A. **127**:647, 1945. (*e*) Horton and Magath.[2]

5. Bain, C. W. C.: Lancet **1**:517, 1938. Sprague, P. H., and MacKenzie, W. C.: Canad. M. A. J. **43**:562, 1940. Schaefer, C. L., and Sanders, C. E.: Am. Heart J. **24**:410, 1942.

6. Gilmour, J. R.: J. Path. & Bact. **53**:263, 1941.

common iliac arteries. He considered the pathologic condition a form of chronic arteritis characterized by multinucleated giant cells—a pathologic picture similar to that seen in temporal arteritis. In the aorta the lesions were widespread; in the carotid arteries the distribution of the lesions was focal, bilateral and symmetric. He reported no involvement of the temporal arteries. Final proof that temporal arteritis is but a local manifestation of widespread arteritis is found in the following reports on the necropsy findings of typical cases: Sproul [7] observed profound changes in the temporal, carotid, innominate, subclavian, pulmonary, celiac, mesenteric, renal and iliac arteries and in the aorta. Chasnoff and Vorzimer [8] reported diffuse involvement of the arterial tree. Cooke and his associates [9] described characteristic pathologic changes in 2 cases, with involvement of the aorta and the temporal, radial, subclavian, femoral, coronary, renal, retinal, celiac and mesenteric arteries.

Temporal arteritis is relatively rare, reports of approximately 40 cases being found in the literature. The rarity of this condition and an opportunity to compare it pathologically with periarteritis nodosa as seen in the material from 7 necropsies prompts us to report our case.

## REPORT OF CASE

A 65 year old white laborer entered the Rochester General Hospital in August 1945, complaining of severe headache and pain over both temporal regions. Eight weeks prior to his admission pain had developed in both thighs. This pain was aggravated by motion and was accompanied by fatigue, malaise and anorexia. Soon afterward he noticed a dull ache in his left shoulder. Two weeks after the onset of his symptoms he was unable to continue on his job and went to bed. Four weeks before admission extreme bitemporal pain and frontal headache developed. Both anterior temporal arteries became swollen and extremely tender, and superficial burning pain was present in the surrounding areas of skin. The pain and the headache were constant but seemed worse at night. Analgesics afforded little relief. The patient stated that he had lost 20 pounds (9 Kg.) in weight during the eight weeks prior to hospitalization.

Before this illness his general health had been excellent. Nocturia had occurred three to four times in the past three years, and there was a vague history of "rheumatism" in the left shoulder.

On admission he appeared pale and gave the impression of a chronically ill patient. The anterior temporal arteries were prominent, enlarged and tortuous (fig. 1). On palpation, both vessels were found to be thickened, tender and faintly pulsating. There were red streaks in the skin about the walls of the left temporal artery. Examination of the eyegrounds revealed no significant pathologic change. The radial and pedal arteries were slightly thickened; their pulsations were forceful and regular at a rate of 80 per minute. His few remaining teeth

7. Sproul, E. E.: New York State J. Med. **42**:345, 1942.

8. Chasnoff, J., and Vorzimer, J. J.: Ann. Int. Med. **20**:327, 1944.

9. Cooke, W. T.; Cloake, P. C. P.; Govan, A. D. T., and Colbeck, J. C.: Quart. J. Med. **15**:47, 1946.

were dirty and carious, with periapical disease and pyorrhea. There was no detectable cardiac enlargement, and the cardiac sounds were faint. The prostate was enlarged to twice normal size and firm. Passive flexion of either thigh produced pain in the groin. The blood pressure was 120 systolic and 80 diastolic. The rectal temperature was 99 F.

The red cell count was 3,590,000 and the white cell count 8,700, with 71 per cent segmented neutrophils, 2 per cent eosinophils, 3 per cent monocytes and 24 per cent lymphocytes. The hemoglobin content was 10.2 Gm. The corrected erythrocyte sedimentation rate was 29 mm. in one hour (Wintrobe), with a hematocrit reading of 32 per cent. Chemical examination of the blood gave the

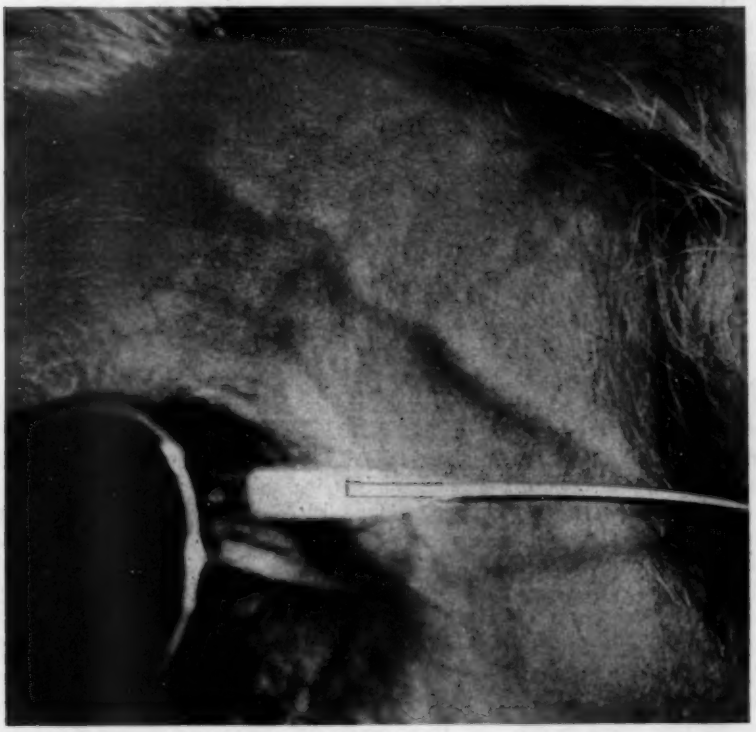

Fig. 1.—Prominent, tortuous, temporal artery of a patient with bilateral temporal arteritis.

following values: blood nonprotein nitrogen 28 mg., blood glucose 79 mg., blood phosphorus 4.6 mg., serum alkaline phosphatase 4.95 units, total serum protein 6.8 mg., serum albumin 3.3 mg. and serum globulin 3.5 mg. per hundred cubic centimeters. Gastric analysis revealed no free hydrochloric acid but a good response following administration of histamine. Culture of material from the throat revealed 80 per cent nonhemolytic streptococci and 20 per cent staphylococci (Staph. albus). Two blood cultures were reported sterile after eight days. Agglutination tests for Bacillus typhosus, Salmonella paratyphi, Salmonella schottmüller and Brucella abortus were reported negative. The Wassermann test of the blood was negative. Urinalysis revealed no significant abnormality.

Roentgenograms revealed a well healed small fibrotic lesion in the apex of the left lung, and no abnormality of the bones of the pelvis or of the upper parts of the femurs. The electrocardiogram showed a normal pattern.

During the first four hospital days the rectal temperature ranged from 99 to 101 F. and thereafter was normal. On the second hospital day the temporal pain subsided rather abruptly, and the pain in the groins subsided slowly over the next

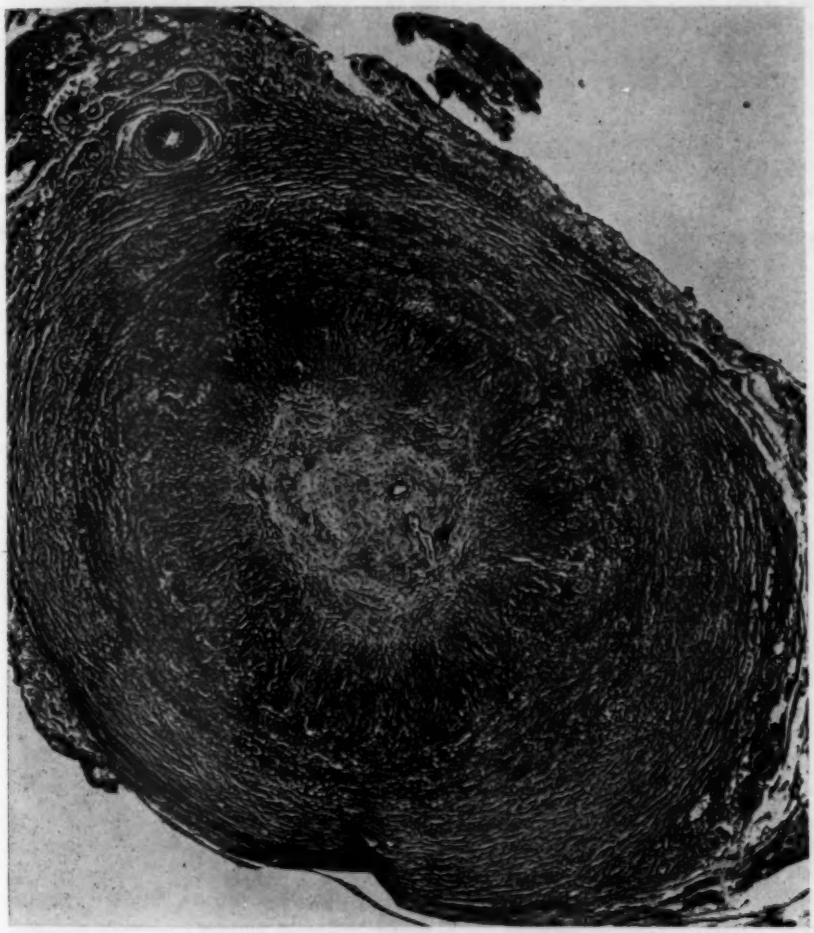

Fig. 2.—Low power photomicrograph of a temporal artery showing diffuse involvement of all coats with almost complete obliteration of the lumen.

fourteen days. The constitutional symptoms improved gradually, and a gain of 5 pounds (2.5 Kg.) was noted when the patient was discharged on the eighteenth hospital day. Biopsy specimens, each about 2 cm. in length, were excised from both anterior temporal arteries on the fourth hospital day.

In April 1946, eight months after hospitalization, the patient returned for a follow-up examination. He had resumed his work as a laborer two months after

being discharged from the hospital and was essentially asymptomatic. He had regained his former weight and strength. The arteries in the temporal regions were no longer visible or palpable; however, pulsations were felt in both main superficial temporal arteries behind the respective temporomandibular articulations. Several laboratory tests were repeated at this time. The blood count showed no anemia. The erythrocyte sedimentation rate was 33 mm. in one hour.

*Histologic Examination.*—Numerous sections of the arterial specimens through all levels revealed essentially similar changes. All layers of the vessel wall were thickened and infiltrated in varying degrees of intensity, predominantly by lymphoid cells (fig. 2). The intima revealed a proliferation of loose connective tissue that completely obliterated the lumen except for a few small recanalized lumens. The connective tissue appeared to be edematous and was infiltrated by small numbers of lymphocytes and plasma cells. The internal elastic membrane was reduplicated, fragmented and completely destroyed in a number of places (fig. 3). The media was edematous and infiltrated by large numbers of lymphocytes, plasma cells

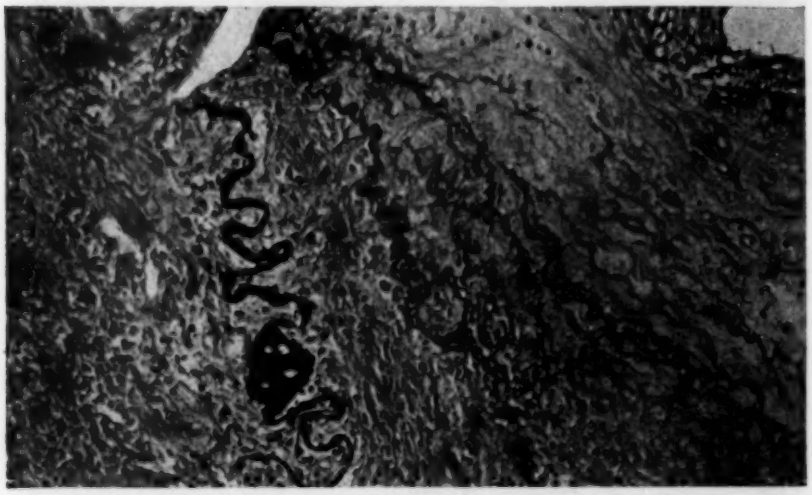

Fig. 3.—High power photomicrograph of tissue prepared with a stain for elastic tissue to show the reduplication, fragmentation and degenerative changes in the internal elastic membrane.

and occasional neutrophil leukocytes. Small focal areas of necrosis were numerous throughout the media, but they showed a definite tendency to be arranged in contact with the internal elastic membrane. About these necrotic areas epithelioid cells were arranged in palisade formation. Moderate numbers of multinucleated giant cells were also present in these granulomatous lesions (fig. 4*A*). There was a dense infiltrate of lymphoid cells in the adventitia, particularly in the form of collars about the vasa vasorum.

## COMMENT

As in most cases of temporal arteritis reported, general malaise, weakness, anorexia and loss of weight were outstanding symptoms in this case. Our patient had the appearance of one debilitated by a long-standing illness. With the recently acquired knowledge that this con-

dition is polyarteritis we find it reasonable to associate these symptoms with the involvement of arteries other than the temporal. This sup-

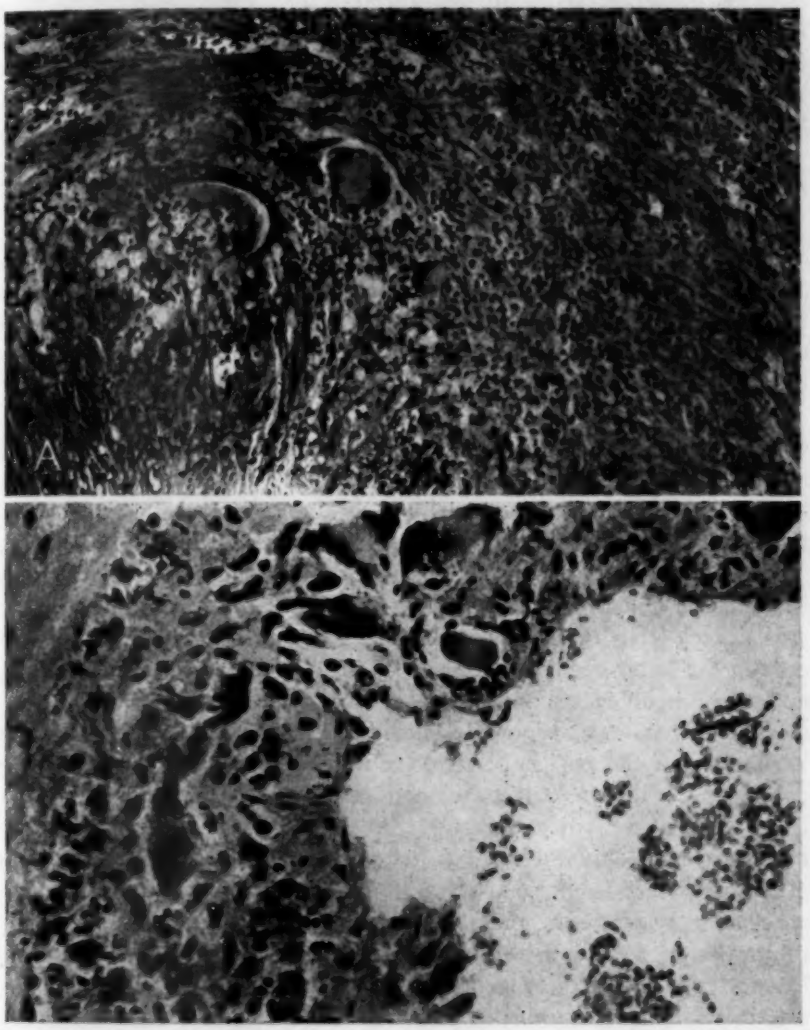


Fig. 4.—*A*, high power photomicrograph of tissue stained by the hematoxylin-eosin method, showing areas of necrosis, epithelioid cells in palisade formation, multinucleated giant cells and diffuse cellular infiltration of the media.

*B*, high power photomicrograph of a section of a coronary artery of a patient with periarteritis nodosa, showing many multinucleated giant cells; hematoxylin and eosin stain.

position is strengthened by the fact that in our case the initial symptom was pain in the extremities. With the appearance of involvement of the temporal arteries, severe headache and extreme bitemporal pain became

the prominent symptoms. The succession of symptoms suggests progressive involvement of different arteries.

The moderate hypochromic anemia, the slight leukocytosis, the increased sedimentation rate and the moderately elevated temperature are frequent findings that have suggested to many an infectious basis for temporal arteritis. As in all other attempts, our bacteriologic and serologic studies revealed no bacterial agent.

It is to be noted that in our case the bitemporal pain had subsided before the biopsy specimens were taken.

### A COMPARISON OF TEMPORAL ARTERITIS AND PERIARTERITIS NODOSA

In the following discussion we proceed on the assumption that it is valid to include with the typical cases of temporal arteritis those cases in which necropsy revealed involvement of the aorta and its large branches, with or without involvement of the temporal arteries.

Horton and his associates [10] described temporal arteritis as a form of periarteritis and arteritis characterized by granuloma-like lesions of the adventitia, by round cell infiltration about the vasa vasorum of the adventitia and by similar but less extensive infiltration of the media. They found hemorrhages in the media and marked intimal thickening in many places. They expressed the view that the lesion probably began as periarteritis in a small segment of the affected artery. This pathologic picture, they said differs from that of periarteritis nodosa in that the inflammatory cells in the latter occur in the form of nodules in the wall of the vessel, and these nodules are made up of collections of mononuclear, polymorphonuclear and eosinophil leukocytes, but they asserted giant cells have not been observed in periarteritis nodosa. Another difference, they pointed out, is that in periarteritis nodosa necrosis of the media frequently leads to formation of aneurysms. Aneurysm formation has not been reported in unequivocal cases of temporal arteritis. We feel that the differentiation of temporal arteritis from periarteritis nodosa on the basis of cellular response in the two conditions is impossible. A diffuse infiltration of the vessel wall in which polymorphonuclear and eosinophil leukocytes participated is mentioned in a number of reports on temporal arteritis.[11] Furthermore, the presence of multinucleated giant cells in periarteritis nodosa has been reported in the literature. A brief search revealed 2 cases.[12] Undoubtedly, a more thoroughgoing search would

10. Horton, B. T.; Magath, T. B., and Brown, G. E.: Arch. Int. Med. **53**:400, 1934.

11. Hoyt, L. H.; Perera, G. A., and Karwar, A. J.: New England J. Med. **225**:283, 1941. Kilbourne, E. D., and Wolff, H. G.: Ann. Int. Med. **24**:1, 1946. Bowers.[3]

12. Krahulik, L.; Rosenthal, M., and Loughlin, E. H.: Am. J. M. Sc. **190**: 308, 1935. Haining, R. B., and Kimball, T. S.: Am. J. Path. **10**:349, 1934.

reveal a higher incidence. Among our 7 cases of periarteritis nodosa 2 showed the presence of giant cells. The section reproduced in figure 4 *B* was cut through a coronary artery of a 17 year old boy in a typical case, with extensive involvement of most of the visceral arteries.

Cooke and his associates stated that in some specimens it was impossible to make a distinction between temporal arteritis, periarteritis nodosa and thromboangiitis obliterans; however, they did make certain generalizations. With regard to periarteritis nodosa they stated:

> . . . The reaction is of acute inflammatory character, and the necrosis of the vessel wall tends to be of a suppurative nature. In temporal arteritis necrosis is found apart from inflammation, and when inflammation is found it is rarely more than subacute. This inflammatory reaction appears to spread axially, as opposed to the focal nature of periarteritis nodosa.

We find no validity in this generalization. The lesion in periarteritis nodosa is never suppurative. Pyogenic bacteria are not found, and the cellular infiltrate does not form pus. The term "suppurative" evidently is used to describe the dense leukocytic infiltration often seen in periarteritis nodosa. As already mentioned, a similar infiltration of the entire wall of the vessel has been observed a number of times in temporal arteritis. Characteristically, periarteritis nodosa presents a great variety of histologic pictures. This variety is determined by the fact that the pathologic process goes through both destructive and reparative phases, and furthermore certain aspects of the histologic picture are the resultant of the rate of destruction and repair. Initially the lesion in periarteritis nodosa is often characterized by medial necrosis associated with little or no inflammatory exudate. This phase is followed by an acute inflammatory reaction, often involving the entire wall of the artery, with polymorphonuclear neutrophils, sometimes many eosinophils, lymphocytes, plasma cells and occasionally giant cells. Reparative phases follow, with proliferation of fibroblasts and formation of granulation tissue. In occasional cases a healed phase with scar tissue may be found. The pathologic pictures of temporal arteritis already described, strongly point to similar destructive and reparative phases. Obviously it is invalid to choose one phase in a pathologic process and label it as the only one representative of that condition. The picture of necrosis with little or no inflammatory reaction described by Cooke and his associates is no more and no less typical for temporal arteritis than the dense inflammatory reaction described in other reports; the same is true of periarteritis nodosa. We are convinced that every histologic picture described in temporal arteritis so far can be found in periarteritis nodosa.

The axial spread in temporal arteritis as opposed to the focal nature of periarteritis nodosa requires little comment. As is well known, the focal or nodose character is not always present. In one of our cases the gross diagnosis was missed at necropsy despite the clinical diagnosis

of periarteritis nodosa. The microscopic sections revealed diffuse involvement with no tendency toward nodule formation. Also it is of interest to note that Gilmour described the distribution of lesions of the carotid arteries in his group of cases as being focal.

There are important differences between temporal arteritis and periarteritis nodosa. Whether these differences are due to different causative factors cannot be answered at present. However, the differences are such as to have value in diagnosis and prognosis and for practical reasons they justify considering the two as separate entities. The differences are found in the distribution of the lesions, in the age and sex groups involved and in the mortality rates.

Periarteritis nodosa involves the visceral arteries and only less commonly a few of the medium-sized and smaller peripheral arteries. We could find no reference in the literature on periarteritis nodosa, available to us, of involvement of the aorta or its primary peripheral branches or both. From the few reports of necropsies it is apparent that the visceral arteries may be involved in temporal arteritis but that the predominant involvement is found in the aorta and in its large branches, such as the innominate, carotid, subclavian and iliac arteries and others.

Temporal arteritis is observed twice as frequently in women; however, no great significance should be placed on this sex difference in so small a group. The age group is striking, for in no unequivocal case, reported has the patient been below the age of 55. In striking contrast, periarteritis nodosa occurs at all ages and is most frequent in young adult males.

That the different distribution of lesions determines the different prognosis of each condition can only be a surmise, but the fact remains that periarteritis nodosa is usually a fatal condition, reports of recovery being extremely rare. Although the generally assumed favorable prognosis of temporal arteritis is no longer tenable, a large proportion of the patients do recover.

The term "periarteritis nodosa" and "temporal arteritis" are inadequate in that they do not describe the essential elements of the conditions to which they are applied and should distinguish as entities. Periarteritis nodosa is rarely only periarteritis; the nodose character, although commonly present, is not essential in the delimitation of this from other forms of arteritis, and not infrequently it is entirely absent. Similarly, temporal arteritis is not limited to the temporal arteries, and what is even more disconcerting, the temporal arteries may not be involved. At present the nomenclature, of necessity, must remain on a descriptive level, and herein lies the difficulty. Logically periarteritis nodosa might be renamed "panarteritis predominantly of the visceral arteries" and temporal arteritis "panarteritis predominantly of the aorta and its peripheral branches." Obviously such terms are awkward and not acceptable.

Furthermore, the original terms have become fixed in the minds of physicians and are associated with definite clinical pictures. We strongly suspect that despite their shortcomings the original terms will be maintained.

## CONCLUSIONS

Both periarteritis nodosa and temporal arteritis go through destructive and reparative phases; histologic pictures essentially similar to those described in temporal arteritis can be seen in periarteritis nodosa.

The distribution of lesions is different in the two conditions. Essentially, periarteritis nodosa is panarteritis predominantly of the visceral arteries, and temporal arteritis is panarteritis predominantly of the aorta and its peripheral branches.

The sex and age groups involved and the mortality rates of the two conditions are different.

# LESIONS OF RETICULOENDOTHELIAL CELLS IN ANAPHYLACTIC SHOCK

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SAO PAULO, BRAZIL

A FOREIGN PROTEIN parenterally introduced into an organism previously treated with the same substance may give way to general manifestations of hypersensitivity or local inflammatory changes similar to those observed in the Arthus phenomenon.

Though the occurrence of a lesion of an individual cell has been admitted for a better understanding of the anaphylactic reaction, no morphologic substratum has been evidenced. In fact, a change in the structure of a cell consequent to a specific hypersensitivity reaction has not yet been demonstrated. Therefore, the point of the problem would be to know whether an anatomic cell lesion is produced in the sensitized animal by the direct attack of the antigen introduced again into the organism. Moreover, there also remains open the question whether all cells are sensitized on the injection of a foreign protein or whether only the elements of certain organs or tissues react to the antigenic substance.

Opie [1] suggested that the cells of a sensitized animal could be attacked and injured as the result of coming in contact with the antigen. He admitted that in the Arthus phenomenon the damage of tissue was due to the toxic effect of the precipitate formed by the interaction of protein and the serum of the sensitized organism.

Later Klinge,[2] injecting protein intravenously in organs isolated from rabbits previously treated, observed phenomena of necrosis in the lymphoid follicles of the spleen. This observation was followed by the experiments of Meyer and Lowenthal.[3] These authors made cultures of splenic tissue and lymph nodes of guinea pigs that had been sensitized by horse serum, in a medium containing this antigen, but could not observe any lesion or disturbance of the growth of the fibroblasts or the reticuloendothelial elements. Identical results were obtained with cultures of endothelial tissue. They also obtained normal cultures with organs of animals which had died from anaphylactic shock.

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From the Department of Pathology, Instituto Biologico.

1. Opie, E. L.: J. Immunol. **9**:259, 1924.
2. Klinge, F., cited by Doerr: Ztschr. f. Hyg. **118**:623, 1936.
3. Meyer, K., and Lowenthal, H.: Ztschr. f. Immunitätsforsch. **54**:420, 1927.

Contrary to these observations, Aronson [4] referred to the results obtained by Sereni and Garofolini, who had noted cell degeneration and death when small quantities of horse serum were added to the culture medium of explants of spleen, bone marrow and omentum of sensitized chicks. Afterward observations were made by Rich and Lewis [5] on allergy in tuberculosis. A clearly noxious effect of tuberculin was observed on cultures of washed blood and splenic cells. Working with transplants of spleen and bone marrow, Aronson confirmed these results. On the other hand, he admitted the possibility that the mechanism of the reaction to tuberculin may be different from the mechanism of anaphylactic shock and of the Arthus phenomenon. More recently Rich and Follis [6] reported that there was no reactivity of individual cells in that allergic phenomenon.

The present work deals with experimental results which indicate morphologic changes and death of certain cells of the organism consequent to hypersensitivity reactions. It was apparent that elements of the reticuloendothelial system were damaged and killed when a foreign protein of nonbacterial provenience was inoculated in an animal previously sensitized by this same substance.

In previous experiments it had been noticed that intraperitoneal inoculation of normal horse serum into guinea pigs sensitized by this antigen produced a state of anaphylactic shock, symptomatologically of the protracted type. Within approximately five to ten minutes after the intraperitoneal injection of 2 cc. of serum, symptoms of shock develop in these animals, such as emission of feces and urine, cough, scratching of the nose and signs of agitation, followed afterward by a manifest state of somnolence and ill feeling. Then the signs of depression increase, and there is progressive lowering of temperature, with purpling of the ears. The evolution of the symptoms is not rarely followed by death one hour or more after the inoculation of the antigen. Other animals, after the development of identical symptoms, slowly and progressively become normal again within two or three hours.

The animals which had died from shock displayed organic changes, such as slight pulmonary emphysema, marked congestion of the liver, sometimes regional circulatory disturbances or acute tumefaction of the spleen, severe hemorrhage in the grastric mucosa and hemorrhage in the subserosa of the intestine, especially in the colon.

These observations were the basis of the present investigations. We started from the idea that probably in this kind of shock the antigen is kept in long and intimate contact wtih the tissues.

4. Aronson, J. D.: J. Immunol. **25**:1, 1933.

5. Rich, A. R., and Lewis, M. R.: Bull. Johns Hopkins Hosp. **50**:115, 1932.

6. Rich, A. R., and Follis, R. H., Jr.: Bull. Johns Hopkins Hosp. **66**:106, 1940.

### EXPERIMENTAL PROCEDURE

Guinea pigs weighing about 250 Gm. were sensitized by injection of 1 cc. of a 1:10 dilution of normal horse serum in saline solution. From twenty to twenty-two days after the sensitizing injection, the shock was brought about by means of an intraperitoneal injection of 2 cc. of horse serum. All the guinea pigs displayed definite symptoms of shock, and some of them died within one hour after the shocking injection. From the animals which died, fragments of liver, spleen and lymph nodes were collected immediately, placed in small sterile flasks containing Tyrode's fluid and kept in the incubator at 37 C. The other animals, which survived, were killed after one hour, and material was collected in the same way under the same conditions.

The material was kept in the incubator for five, six, seven, eight, ten, eleven, eighteen and twenty hours, then taken out and fixed with Heidenhain's fluid for three or four hours, embedded in paraffin and stained with hematoxylin-eosin.

In another series the animals were killed two, three, five, six, seven, eight and nine hours after the onset of the shock and their tissues immediately fixed with Heidenhain's fluid.

The control animals were not sensitized but received 2 cc. of serum intraperitoneally.

Eighty-three guinea pigs were used, 25 of which were controls.

### OBSERVATIONS

*Liver.*—The liver of sensitized animals that died from shock or were killed approximately one hour after the injection did not show significant changes. Only a slight enlargement of the nuclei of the endothelial cells of the sinusoids could be observed. However, in the sensitized animals that were killed after three or more hours, changes as described later were evident. This was true also in the surviving tissue prepared according to the technic just described. It was possible to note that the state of nuclear tumefaction observed at first was only the initial phase of a heavy damage of the Kupffer cells. These slight initial manifestations developed within about three hours after the initiation of shock. In some cases numerous cells showed the nucleus in a stage of extreme tumefaction, resembling a bladder or a balloon, and surrounded by a thickened, clearly visible membrane. The impression obtained was that the substances contained in the nucleus were pressed close to the membrane, thus giving the picture of peripheral hyperchromatosis, which I like to call "shell nucleus." Such a change seems to be incompatible with the cell's life; the phenomenon is irreversible, and this stage is probably followed by a phase of disintegration. As a result, either signs of lysis of the thickened membrane or the striking picture of nuclear rupture can be observed. It could be verified that, probably owing to an excessively high internal pressure, the rupture of the membrane sometimes occurs, the content being expelled. The nucleus then gets a shriveled appearance and finally disintegrates.

These phenomena could be distinctly observed from three to seven hours after the occurrence of the shock. It must be emphasized, however, that such intense alterations were found quite rarely; generally the lesion observed was of the same type but more discrete, although ending with nuclear lysis. Even no cell reaction was observed in some cases. On the other hand, the lesion was not generalized among the elements of the same organ; in many cases practically resting, normal cells were seen among others with more or less marked reaction.

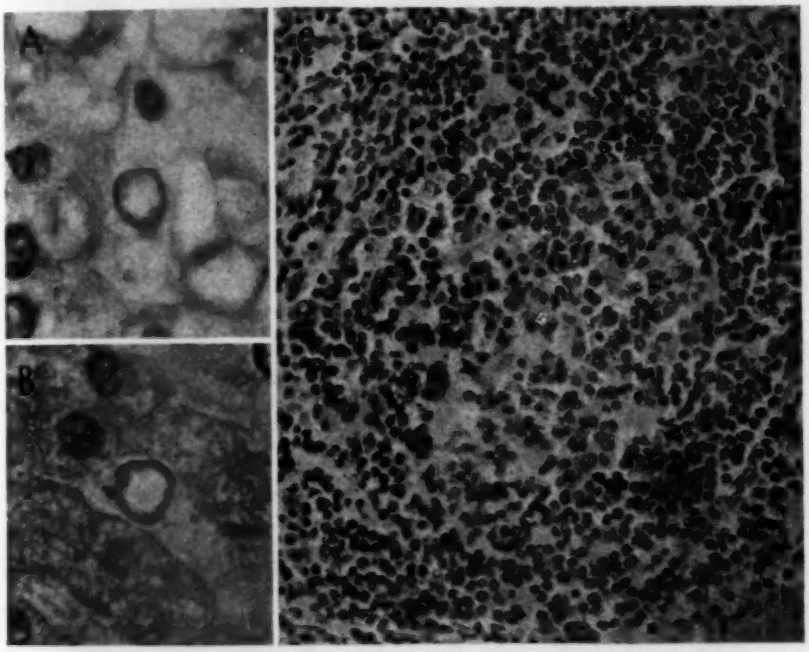


Fig. 1.—*A*, liver fixed five hours after the shock-inducing inoculation. Kupffer cell with heavy tumefaction of the nucleus beside an element which is at rest. × 1.050; Zeiss objective.

*B*, liver maintained in the incubator for six and a half hours (eight and a half hours after the shock-inducing injection). The Kupffer cell's nucleus has a bladder-like aspect. Compare it with the nuclei of the hepatic cells. × 1.050; Zeiss objective.

*C*, spleen fixed five hours after the shock-inducing injection. A lymphoid follicle is shown with numerous cells in a state of necrobiosis. × 280; Zeiss objective.

Only certain changes, probably of secondary significance, could be noted in the liver cells. They appeared larger and more turbid and showed less affinity for stains than normal liver cells.

In control animals, not previously sensitized, the intraperitoneal injection of serum did not cause the development of a picture similar to that described. The material of these animals, studied under the

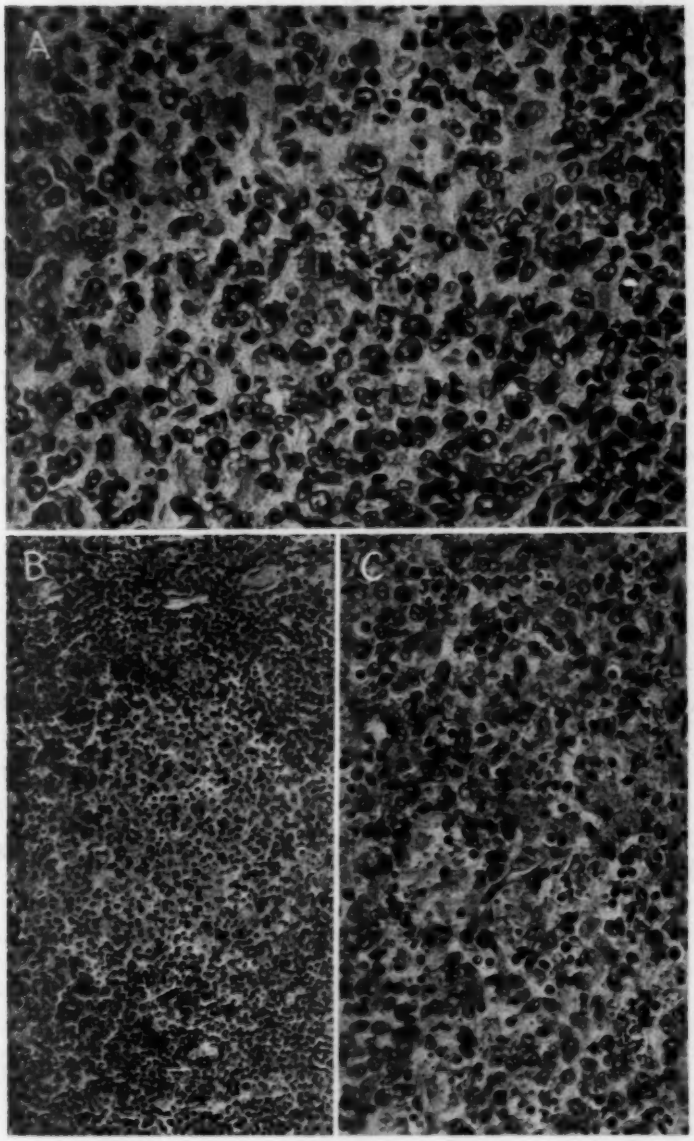


Fig. 2.—*A*, spleen fixed seven and a half hours after the shock-inducing inoculation. A secondary follicle is shown. Note disintegrating cells and cell particles. × 450; Zeiss objective.

*B*, lymph node fixed seven hours after the shock-inducing injection. A secondary follicle is seen, distinctly rarefied. × 150; Zeiss objective.

*C*, lymph node fixed eight and a half hours after the shock-inducing inoculation. A secondary follicle with numerous disintegrating elements is shown. Nuclear pyknosis. × 320; Zeiss objective.

same conditions, showed only a slight state of engorgement of the Kupffer cells, and occasionally one or another element attained a more advanced phase of tumefaction without showing any change in its structure.

At this point I must refer to a detail important for these observations. The technic of maintaining the animal alive for varying lengths of time could not be employed throughout all the successive studies of cell changes, for at the beginning a marked decrease in the number of recognizable Kupffer cells was evident in animals killed four or five hours after the occurrence of the shock. (The combined use of both technics appeared therefore of advantage.)

These elements after being altered were possibly drawn along by the circulation, only the undamaged cells being kept by the liver. If the process of maintaining the organ in vitro is used, that inconvenience is avoided, the cells being "in loco" for further observation.

*Spleen.*—Cell changes were also noted in the spleen, but only in the cells of the germinative centers of the follicles. These lesions were observed in various phases. Examination with low magnification showed in these cases an evident change in the structure of the follicles; the germinative centers appeared clearer than usual and as if they were rarefied. With higher magnification a distinct cell reaction could be perceived. The cells of the germinative centers seemed more intensely damaged. Cells with large and clear nuclei were scantily scattered throughout the follicle. The nuclear enlargement was of the same extent as that in the Kupffer cells and was also associated with nuclear hydrops and signs of peripheral hyperchromatosis. In later stages lysis of the membrane or signs of nuclear rupture were also noted. Some of the cells displayed distinct pyknosis; others, karyorrhexis and karyolysis.

Finally, I must refer to the absence of reaction of the reticuloendothelial cells of the red pulp. In these elements only slight enlargement of the nucleus was observed.

In the control animals no changes of the lymphoid follicles were observed.

*Lymph Nodes.*—Submaxillary, retropharyngeal prescapular and inguinal nodes were studied. Cell changes of varying intensity were frequently observed, mainly in the follicular and extrafollicular germinative cells of the cortex.

The large and clear follicular cells and the young reticular elements scattered throughout the cortical layer were most intensively damaged. Usually the most extensive changes were present in the secondary follicles. The picture of cell reaction, with distinct enlargement of the nucleus, was identical with that described in the spleen. Cells which

seemed to be lymphoblasts showed a different kind of reaction, leading to pyknosis and nuclear fragmentation.

No reaction could be observed in other reticuloendothelial elements of the lymph nodes; neither the endothelial cells of the lymphatic sinuses nor the reticular cells of the medullary cords showed any important sign of damage of their structure.

In the control animals the follicles and other portions of the cortex and the medulla showed no significant changes.

## COMMENT AND SUMMARY

The cell changes described might be interpreted as a consequence of the antigen-antibody reaction in the organism of the sensitized animal. Lesions have been observed only in a certain type of reticuloendothelial cells, mainly in the Kupffer cells. The significance of this observation cannot be definitely ascertained at the present time. It may be, however, more than a coincidence that the only type of cells found injured after the shocking injection were those which have been credited with playing a role in the formation of antibodies, namely the reticuloendothelial [7] and the lymphoid cells.[8]

7. Sabin, F. R.: J. Exper. Med. **70**:67, 1939.

8. Harris, T. N.; Grim, E.; Mertens, E., and Ehrich, W. E.: J. Exper. Med. **81**:73, 1945.

# CAROTID-CAVERNOUS FISTULA

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THE INTERNAL carotid, after it has passed through the carotid canal in the petrous portion of the temporal bone, enters into the cavernous sinus. Here the artery is adherent to and extends along the entire length of the lateral wall of the sinus. The artery is separated from venous blood only by the endothelial lining of the sinus. The cavity of this sinus, which is irregular in shape and size, is so divided by numerous fibrous strands that it assumes the appearance of cavernous tissue.[1] The oculomotor, the trochlear, the ophthalmic and the abducens nerves and the gasserian ganglion are also within the sinus. It has been known for many years that the portion of the internal carotid artery within the cavernous sinus occasionally ruptures. This lesion is most frequently described under the title "Pulsating Exophthalmos."

Travers [2] was apparently the first to describe this condition, in 1809. Since that time more than 800 cases have been described, and in 1943 Martin and Mahon [3] studied the entire literature subsequent to Locke's [4] extensive review in 1924. From the standpoint of pathology, however, relatively little has been written on the lesions present in patients with this condition. Baron [5] was the first to perform an autopsy in which a fistula between the internal carotid artery and the cavernous sinus was demonstrated. Subsequently, additional cases examined at autopsy have been described, and these have been reviewed by Dandy.[6] He stated that up to 1937 29 postmortem specimens had been described, most of them in foreign literature. Since that time Bergstrand,[7] Sugar and Meyer [8] and Cunningham [9] have each reported an additional case. Dandy and Follis [10] have written an excellent article devoted mainly to the pathologic aspects of carotid-cavernous fistula, in which they describe 2 additional cases.

1. Young, A. H., and Robinson, A., in Cunningham, D. J.: Cunningham's Text Book of Anatomy, ed. 6, New York, Oxford University Press, 1931, p. 989.
2. Travers, B.: Med.-Chir. Tr. **2**:1, 1813.
3. Martin, J. D., Jr., and Mahon, R. F.: J. A. M. A. **121**:330, 1943.
4. Locke, E. C., Jr.: Ann. Surg. **80**:1, 1924.
5. Baron: Bull. Soc. d'anat. de Paris, 1835, p. 178.
6. Dandy, W. E.: Zentralbl. f. Neurochir. **2**:77, 1937.
7. Bergstrand, H.: Acta radiol. **18**:58, 1937.
8. Sugar, H. S., and Meyer, S. J.: Arch. Ophth. **23**:1288, 1940.
9. Cunningham, J. C.: J. Iowa M. Soc. **32**:495, 1942
10. Dandy, W. E., and Follis, R. H.: Am. J. Ophth. **24**:365, 1941

A fistulous opening in the internal carotid artery within the cavernous sinus is undoubtedly the most common cause of "pulsating exophthalmos." Nevertheless, it should be pointed out that other lesions can be associated with this syndrome. Occasionally other lesions of the internal carotid artery are found. These include aneurysms outside the cavernous sinus,[11] also arteriovenous aneurysms, with the jugular vein most often found in the carotid canal. In a few instances an aneurysm of the carotid artery in the cavernous sinus without evident rupture [9] has been found with pulsating exophthalmos. In such cases it is possible that a minute opening may have existed during life. Pulsating exophthalmos may be the result of intraorbital lesions. These include simple aneurysms of the ophthalmic artery, intraorbital arteriovenous aneurysms and, more rarely, other intraorbital tumors. Other causative conditions are meningocoele, absence of a large part of the orbital roof, intracranial tumors and other tumors extending into the orbit.[12]

In approximately 75 per cent of cases of pulsating exophthalmos trauma is considered to be the important etiologic factor. It is to be expected that in virtually all of these there will be a carotid-cavernous fistula, and Locke [4] found such a fistula in 16 of 17 cases examined by autopsy. Usually a fairly severe blow to the head precedes symptoms by several or many hours. The internal carotid artery, as well as the cavernous sinus, is immobile, and a sharp blow may cause rupture of the artery with or without fracture of the adjacent sphenoid bone. Arteriosclerosis of the artery increases the likelihood of rupture in such cases. Nevertheless, ruptures can occur in young people in whom little or no sclerosis is observed.

Approximately 25 per cent of cases of pulsating exophthalmos are nontraumatic, and only about half of these have carotid-cavernous fistula as the cause. The most important etiologic factor in this group is sclerosis of the internal carotid artery. Parry and Rogers [13] reported that a patient of theirs had aneurysm formation after violent sneezing; hence increased blood pressure may be an added factor. Undoubtedly, another factor is of importance in these situations, since it is most unusual for spontaneous openings to form in medium-sized arteries. The anatomic relationships here are unique, and it may well be that lack of tissue support of the internal carotid artery within the sinus increases the likelihood of the formation of a fistulous opening. Although some stress has been given to the position and the size of these openings in regard to severity of exophthalmos, Dandy and Follis [10] expressed the belief that no definite relationship exists. That some fistulas are

11. Ellis, N. B.: Texas State J. Med. **35**:483, 1939.
12. Harkness, G. F.: Internat. J. Med. & Surg. **43**:243, 1930.
13. Parry, R., and Rogers, L.: Brit. J. Surg. **27**:179, 1939.

the result of ruptured "berry" aneurysms is possible but may be difficult to prove. Dandy and Follis [10] in 1 case found such aneurysms in the circle of Willis and postulated that the opening within the sinus may have been the result of rupture of an aneurysm. According to Dandy,[6] no case of proved congenital arteriovenous aneurysm has been found at autopsy. Although syphilis has been suspected, it apparently has not been found at postmortem examination.[4] As would be expected, the average age of the patients with spontaneous fistulas is approximately fifteen years higher than the age of those whose aneurysms are produced by trauma.[4]

The primary lesion of a carotid-cavernous aneurysm is an opening in the wall of that portion of the internal carotid artery which is within the cavernous sinus. These lumens have been found to vary from 1 or a few millimeters to actual absence of the artery over a distance of a centimeter or more. More than one opening is occasionally found. Frequently there is ectasia or an actual aneurysm of the artery. Occasionally, abnormal twists are found. In cases produced by trauma little sclerosis may be present. Microscopically, there is a variable degree of intimal fibrosis and thickening, often with cholesterol deposits and calcification. The media is usually definitely thinned, and elastica stains show extensive irregularity and fraying of the internal elastic lamina and other elastic layers with focal areas of complete destruction. Usually little inflammation is noted.

The cavernous sinus is likely to be markedly distended by blood, and the various normal septums are consequently distorted or destroyed. Mural thrombi may be present within the sinus. The intraorbital veins are usually also greatly distended. The intercavernous, the basilar and the superior and inferior petrosal sinuses may all be expanded. Not infrequently the opposite cavernous sinus is dilated as well. This occurs particularly in those cases in which the intercavernous sinus is large and widely patent. The nerves within the sinus are usually flattened or may be interrupted. The gasserian ganglion is elevated and pushed laterally, depending on the amount of distention of the sinus. The pituitary gland and the optic nerves may be compressed, and in some cases atrophy of the latter is found.

The pathologic changes found in the brain vary greatly. Frequently, but not always, free blood is found in the subdural space. Occasionally also there is subarachnoid hemorrhage, which may be prominent over the cerebellum.[10] Sugar and Meyer [8] reported intraventricular hemorrhage as well as intracerebellar hemorrhage in their postmortem specimen. There can be extensive encephalomalacia involving most of one hemisphere as observed by Karplus.[14] Cunningham [9] noted encephalomalacia

14. Karplus, P.: Wien. klin. Wchnschr. **13**:357, 1900.

with hemorrhage. Dandy and Follis [10] reported petechiae within the cortex of the frontal lobe in 1 case, but without change in the ganglion cells. In their other case there was encephalomalacia due to old infarcts involving the right frontal lobe and basal ganglions (the fistula was also on the right). A more recent infarct was found involving both cerebral peduncles, and petechiae were present in the island of Reil. Additional recent infarcts were also noted within the pons. It is evident therefore that lesions within the brain may be minimal or abundant and may or may not be directly associated with the cause of death.

The mechanics of the circulation following rupture of the internal carotid artery within the cavernous sinus are relatively simple. There is a transfer of arterial pressure to the sinus, which then becomes dilated, with rupture of its various septums. The blood flow reverses within the superior ophthalmic vein, which begins to dilate and pulsate. Smaller orbital veins become similarly involved. This results in pulsating exophthalmos and frequently edema and even hemorrhage within the tissues about the eye. The petrosal sinuses probably drain away most of the blood from the cavernous sinuses. The nerves within the cavernous sinus and the optic nerve may be stretched or compressed; hence loss of vision and extraocular palsies may occur. Further complications within the vascular system frequently set in. Sattler [15] in a study of 235 cases found bilateral pulsating exophthalmos present in 17 per cent. In these cases it is postulated that either by way of the intercavernous or the basilar sinus blood is forced into the opposite cavernous sinus. This has been substantiated at autopsy.[10] The intercavernous sinus is the most direct connection, and when it is relatively large, bilateral exophthalmos is apt to develop readily. In other cases this sinus apparently widens gradually, and exophthalmos of the opposite side develops a week or more later. In view of the usual presence of an intercavernous sinus it is of interest that in most cases pulsating exophthalmos is not bilateral. This can be explained only on the basis that the connecting channels are small or absent. A few cases of contralateral exophthalmos have been observed—for instance, that reported by Geis [16] and that by Dandy and Follis.[10] The latter was proved by autopsy. The lack of ipsilateral exophthalmos was found to be due to a thrombus of the ophthalmic vein. The intercavernous sinus was widely patent, and the opposite cavernous sinus was also greatly dilated. Another possible cause of this condition might be congenital absence of the ipsilateral superior ophthalmic vein with a widely patent intercavernous or basilar sinus. It is of interest that in the case observed by Dandy and Follis bilateral exophthalmos was noted in a previous

15. Sattler, C. H., cited by Dandy.[6]

16. Geis, F.: Klin. Monatsbl. f. Augenh. **106**:209, 1941.

hospital visit. Thrombosis therefore apparently cured the exophthalmos on one side.

### REPORT OF A CASE [17]

Mrs. L. G., a 61 year old white woman, was admitted to the hospital in coma. She had become suddenly comatose about twenty hours before admission. She was incontinent but moved her limbs freely. Previous to this the patient had several periods of unconsciousness from which she recovered in about five minutes. This had been noted for approximately six weeks. There were also gradual loss of hearing, aphasia and change in personality. The past history revealed that the patient had a "stroke" in her left eye several months before. In addition, she had a cataract removed from the right eye approximately seven weeks previously.

The patient was comatose, with dry, loose skin. There was some hyperemia of the conjunctivas. The right eye showed an irregularity of the iris, presumed to be due to the previous operation. No exophthalmos was noted, and both eyeballs had normal tension. There was some dilatation of the left pupil, and no response to light was noted. The neck was slightly stiffened. No significant changes were noted in the thorax and the abdomen. There was no paralysis of the extremities, Babinski's reflex was not present, and the other reflexes were average. The blood pressure varied from 125 systolic and 55 diastolic to 124 systolic and 90 diastolic.

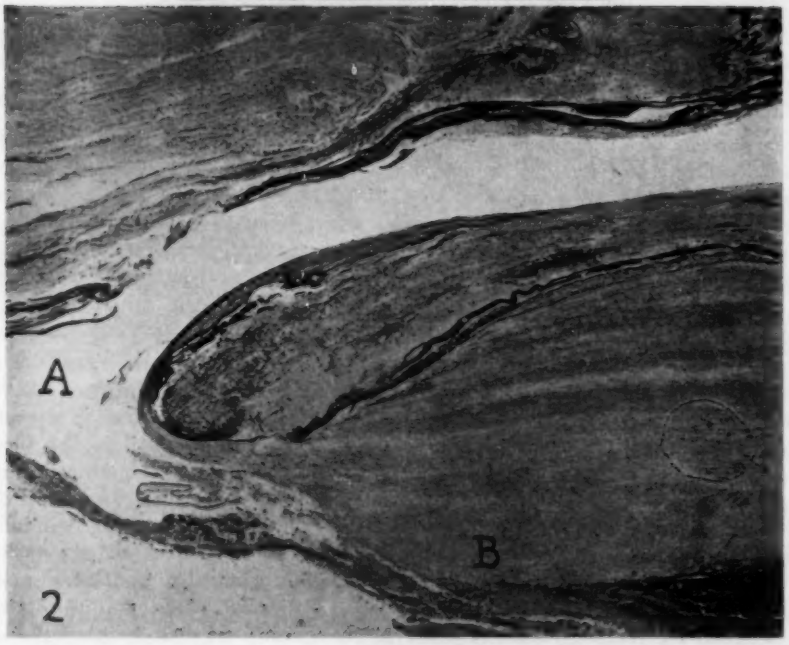
Urinalysis revealed albumin (2 plus) and a moderate number of leukocytes in the sediment. The red blood cell count was 3,600,000 and the hemoglobin value 11.9 Gm.; the white blood cell count was 9,800. The blood urea was 42 mg. and the blood sugar 106 mg. per hundred cubic centimeters. The spinal fluid was clear, with a 4 plus precipitate in the Pandy test. The Nonne-Appelt phase I was 2 plus, and phase II was 3 plus. The protein was 67 mg. per hundred cubic centimeters of fluid. The mastic test was 444420, and the Kline exclusion and diagnostic tests were negative.

The patient partially regained consciousness the day after admission and for several days was able to answer questions slowly and move her extremities. Gradually her condition became worse, and she died on her sixteenth hospital day.

*Autopsy.*—The only external features of note were medial deviation of the left eyeball and dilatation of the left pupil (9 mm.) and an irregularity of the right pupil, presumably due to a previous operation. No proptosis was noted. The heart weighed 200 Gm. and was moderately dilated. There was marked calcification of the cusps of the aortic valve with formation of an acquired bicuspid valve. Only slight thickening without deformity of the mitral and tricuspid leaflets was noted. The coronary arteries were only slightly sclerotic. The aorta showed marked sclerosis. The lungs were hyperemic and emphysematous. There was an obsolete primary tuberculosis complex involving the upper lobe of the left lung and the corresponding bronchopulmonary lymph node. The liver and the spleen were hyperemic and contained obsolete miliary tubercles. The gallbladder contained several calculi. The pancreas, the adrenal glands and the genitourinary tract showed no significant changes except chronic cystitis (cystitis lymphomatosa). There were acute esophagitis and diverticulosis of the sigmoid colon.

The brain weighed 1,250 Gm. There was no subdural or subarachnoid hemorrhage. The leptomeninges were of average thickness, and the gyri and the sulci had the usual configuration. The base of the brain about the tuber cinereum,

17. This case report is made with the permission of Dr. Gannon and Dr. J. F. Slowey.




*1*, photograph of the carotid-cavernous fistula. A black arrow shows the carotid artery cut longitudinally and a white arrow the proximal part cut transversely. At *A* is the opening in the carotid artery, showing the slightly rounded margin. At *B* is the thrombus in the cavernous sinus.

*2*, photomicrograph (× 31) showing a longitudinal section of the internal carotid artery. At *A* is the opening corresponding to *A* in *1*. Notice also the fraying and interruption of elastic fibers. At *B* is the thrombus in the cavernous sinus.

especially to the left, was compressed somewhat by an underlying mass. The optic tract and nerves, as well as the left third, fourth and sixth cranial nerves, were moderately distorted by the same mass. The circle of Willis was complete, and the vessels were of moderate size, showing moderate to marked sclerosis without significant narrowing of the lumen. Similarly the intracranial portions of the internal carotid arteries showed marked sclerosis but without marked lessening of the lumens. Cross section of the brain failed to reveal any gross lesions in the brain substance. The ventricular system was of average size and contained no blood. Microscopically, slight edema of the brain substance was noted, with slight degenerative changes in some of the neurons. These were nowhere severe in degree and were interpreted to be the result of partial ischemia of the brain. No hemorrhage or necrosis was observed, although many sections were taken from all principal portions of the brain.

The left cavernous sinus was greatly distended, measuring 3 cm. superoinferiorly, 3.2 cm. anteroposteriorly and 4.2 cm. mediolaterally. Its external surface was gray and without hemorrhage. The medial portion extended into the sella turcica approximately 5 mm. beyond the midline. The pituitary gland was raised and compressed. The entire optic chiasm was elevated and pushed anteriorly, with distortion particularly of the left optic nerve. Some distortion of the third, fourth and sixth cranial nerves was also noted. The internal carotid artery at its exit from the cavernous sinus was anterior and to the right. Section revealed the enlarged sinus to be filled with clotted blood, which in the inferior and anterior portion was firm, laminated and adherent to the endothelium. The various septums were completely obliterated. The area about the region of the superior ophthalmic vein was completely covered by adherent thrombus. The orbital veins were unfortunately not examined. No portion of the circular sinus could be identified, and the basilar and petrosal sinuses were not dilated. The right cavernous sinus was also not enlarged.

In its course through the petrous portion of the temporal bone the internal carotid artery was of average size. Although there were many intimal plaques, the lumen was only slightly decreased in size. No external variations were noted in the foramen lacerum medium or at the entrance into the cavernous sinus. Within the sinus the artery widened slightly from its average diameter of 5 mm. up to 8 mm. Then its wall became frayed and friable and for a distance of 1 cm. it was completely unrecognizable. At a point 8 mm. from its exit the superior portion of the wall was recognizable, and at the exit it was complete and the lumen was of a diameter similar to that at its entrance.

Microscopically, the wall of the cavernous sinus was composed of collagenous connective tissue. This contained a few foci of hemorrhage and small collections of lymphocytes. A lining endothelium could be demonstrated only in some places. There were adherent thrombi in some areas, but these showed little organization. There was moderate to marked intimal fibrosis and thickening of the internal carotid artery. Its media showed extensive degeneration and actual necrosis. In one area the media had a myxomatous appearance with a neutral stain, but no actual cyst formation was noted. No inflammation was noted. Considerable pyknosis of nuclei was found in some areas. Elastica stains revealed extensive fraying and degeneration of elastic tissue, particularly of the internal elastic membrane, and this was especially marked at the edge of the ruptured portion. In one section the elastica of the artery was slightly reflected over the lining of the cavernous sinus.

## COMMENT

At no time in the hospital was this patient noted to have exophthalmos; hence the true nature of the underlying lesion was not clinically suspected. Certainly, to exclude exophthalmos completely, accurate measurements must be taken; nevertheless, if any was present in this case, it was extremely slight. Both eyes were palpated, and no pulsation was noted. Unfortunately, no attempt was made to hear a bruit. It is surprising, however, that the patient did not complain of noise within her head, for this is a frequent symptom. One lone statement in the history gives a clue indicating that the fistula originated about two months before the patient's admission to the hospital—namely, the statement that the patient had a "stroke" in the left eye at that time. Just what this "stroke" was is not known, but it is possible that she had an actual pulsating exophthalmos at that time which later receded because of thrombosis of the ophthalmic vein. This vein was not examined, because even at the time of autopsy the true nature of the lesion was not suspected. Nevertheless, the thrombus in the anterior and inferior area of the sinus suggests that the vein also was occluded by a thrombus.

Undoubtedly, arteriosclerosis was the most important factor causing rupture of the artery. In a few areas the changes resembled somewhat those found in idiopathic medionecrosis of the aorta, and this may possibly be an additional etiologic factor in the present instance. The defect in the artery was much larger in this than in virtually all previously recorded cases. The cavernous sinus was also dilated more than in some previous cases, although in not many cases is there a record of accurate measurements. The absence of dilatation of the right cavernous sinus can be explained only by absence of, or occlusion by distortion of, the intercavernous sinus and by absence of dilatation of the basilar sinus. The immediate cause of death was undoubtedly a combination of dilatation of the heart and ischemia of the brain. It is of interest that no hemorrhage or infarct was found anywhere within the brain.

## SUMMARY

A patient with a carotid-cavernous fistula in whom no pulsating exophthalmos was noted came to autopsy. The rupture of the carotid artery was extensive. No infarct or hemorrhage was found in the brain.

# TRUNCUS ARTERIOSUS COMMUNIS PERSISTENS

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THERE is no one typical picture of truncus arteriosus communis persistens. Humphreys [1] in 1932 made a careful study of the developmental factors concerned and formulated criteria for the identification of this rare anomaly. These criteria are as follows:

1. Only one large arterial trunk leaves the base of the heart. This is the primary requirement.
2. The arterial trunk must combine the features and the functions of both the aorta and the pulmonary artery, on the one hand giving off the coronary and systemic arteries, and on the other supplying blood to the lungs.
3. The interventricular septal defect is always present.
4. The trunk is commonly in the position of the so-called rider aorta with varying degrees of shift to the right.
5. The surest landmark of the common trunk is its four semilunar valves.
6. The crista supraventricularis proper should stop at the base of the septum, beneath the ostium of the trunk.
7. There is patency of the foramen ovale, varying in degree from case to case.
8. The mitral and the tricuspid leaflets undergo modifications of form and attachment according to the degree of shift of the trunk to the right.

The necessity of four cusps is not accepted by Abbott,[2] Hunter [3] and Lev and Saphir.[4] They require that the large single vessel give rise only to the coronary, pulmonary and systemic vessels.

Before a final diagnosis of persistent common arterial trunk can be made, it is necessary that pulmonary or aortic atresia be rigidly ruled out (Abbott [2]). These atresias occur in cases of truncus solitarius aorticus or pulmonalis, an anomaly in which one trunk functions for both cir-

1. Humphreys, E. M.: Arch. Path. **14**: 671, 1932.
2. Abbott, M. E.: Atlas of Congenital Cardiac Disease, New York, American Heart Association, 1936.
3. Hunter, O. B., Jr.: Arch. Path. **37**: 328, 1944.
4. Lev, M., and Saphir, O.: J. Pediat. **20**:74, 1942.

culations; the other is obliterated, and may be found as a fibrous remnant attached to the base of the heart.

Only 37 of the cases recorded in the literature conform to the foregoing criteria. Abbott [5] in 1927 recognized 23 cases, but in Humphreys' [1] review, published in 1932, only 15 were listed as acceptable. Of these, 5, including 1 of her own, had the theoretically required four semilunar cusps; 3 cases had three cusps and a rudimentary fourth cusp; 7 cases had only three cusps but satisfied many of the other requirements. In 1942 Lev and Saphir [4] compiled 19 additional cases. Other recent contributions were those of Van Brown,[6] Doerr [7] and Hunter,[3] each of whom reported 1 case. The case now reported is the thirty-eighth.

## REPORT OF A CASE

A boy was born in Provident Hospital May 1, 1945. The mother, a secundipara, was 17 years old. Her serologic tests were negative. The first child was living and well. Gestation and delivery were uneventful. The newborn infant's weight was 2,770 Gm. Because of cyanosis and difficulty in breathing, he was placed in an oxygen tent. On the ninth postnatal day a roentgen examination of the chest showed "no significant lesion." Cyanosis and dyspnea continued. On the seventeenth day he was discharged, "not much improved."

He was readmitted November 27, acutely ill, with a history of a severe cold that began ten days previously. On admission his temperature was 97 F. Four hours later it had fallen to 96.4; it then rose rapidly to a peak of 100.4, after which there was a sharp decline to 98.8. The significant physical findings were: marked cyanosis, thick whitish fluid in the throat, purplish discoloration of the oral mucosa, harsh bronchial breathing and a hyperdynamic heart, enlarged to the right. The clinical impression was acute tracheobronchitis and congenital heart disease.

Therapy consisted of the administration of oxygen, nikethamide fluids (parenterally administered) and penicillin. There was no apparent impression on the course of the disease, and death occurred fifteen hours after the infant was admitted to the hospital.

*Autopsy* (thirty-three hours after death).—The anatomic findings, exclusive of those in the heart, were as follows: The body was that of a poorly nourished infant boy, 62 cm. in length and 4,750 Gm. in weight. The skin was loose and wrinkled. The head was symmetric and covered with soft, thin dark brownish hair. The posterior fontanel was closed; the anterior fontanel was patent. There were no erupted teeth. The subcutaneous, omental and mesenteric fat depots were depleted. The stomach and the intestines were distended with gas. There was no free fluid in the abdominal cavity. The peritoneal surfaces were smooth and moist. The lower border of the liver was 2 cm. below the costal margin in the right midclavicular line and 1.5 cm. below the xiphoid process in the midline. The liver was pale brownish and firm in consistency. Its weight with the gallbladder was 185.3 Gm. The other abdominal organs were in their normal positions and showed

5. Abbott, M. E.: Congenital Cardiac Disease, in Osler, W., and McCrae, T.: Modern Medicine, Philadelphia, Lea & Febiger, 1927, vol. 4, p. 612.

6. Van Brown, D.: J. Tech. Methods **22**:101, 1942; cited by Hunter.[3]

7. Doerr, W.: Virchows Arch. f. path. Anat. **310**:304, 1943; cited by Hunter.[3]

no significant gross changes. There was no free fluid in the pleural cavities. The pleural surfaces were smooth and moist. The thymus extended from the thoracic inlet to the ventral surface of the pericardium, to which it was attached. Its weight was 5.3 Gm. The mucosa of the trachea and the main bronchi was hyperemic. These passages contained thick, frothy, grayish white fluid. The left lung weighed 46 Gm. The cut surfaces of both lungs showed patchy, irregular areas, varying in color from grayish yellow to dark red, characteristic of bronchopneumonia.

The heart was approximately in the center of the thorax. The transverse dimension of the pericardium was 7 cm. The right border was 4 cm. and the left border 3 cm. from the midsternal line. The pericardial sac contained 2 cc. of thin amber fluid. Its inner surfaces were smooth and moist. The external surface

Persistent truncus arteriosus communis: anterior view showing the enlarged right ventricle, the single trunk, the patent ductus arteriosus and the septal defect with glass rod inserted.

of the heart was smooth and dull red. The coronary vessels were prominent and slightly tortuous. There were a few small deposits of pale yellowish fat along the courses of these vessels. The right atrium was markedly dilated and contained a soft, pale yellowish clot and some dark red fluid blood. The lining of the right ventricle was smooth, thin and transparent. A 3 mm. probe was readily passed through the patent foramen ovale. The right atrioventricular ("tricuspid") orifice was 4.2 cm. in circumference. It did not have a distinct posterior leaflet. There was a large anterolateral leaflet, as well as a smaller medial leaflet. The anterolateral leaflet was connected by long slender chordae tendineae to the anterior

papillary muscle, which was 3 mm. thick. Lateral to this muscle was another papillary muscle, 1 mm. thick. It was inclined medially and its chordae were attached to the same leaflet.

The medial leaflet was connected to the interventricular septum by several small chordae and to a papillary muscle, 3 mm. thick, which arose from the posterior wall close to the septum. The right ventricle was markedly dilated. Its greatest inner circumference was 4.5 cm., and the distance from the atrioventricular ring to the apex was 3.5 cm. The wall, including the columnae, was hypertrophic, having a thickness of 7 mm. The endocardium was smooth, thin and transparent. The myocardium was dull red and firm in consistency. The interventricular septum was defective in its upper membranous edge. This spheroidal septal defect was 10 mm. in its greater transverse diameter and 7 mm. in the lesser superior-inferior dimension. In the rider position, immediately above the defect, was the ostium of the one great vessel from the heart. The ostium was 3.5 cm. in circumference and was approximately two thirds over the right ventricle. The myocardial fibers of the ventricle apparently terminated in a fibrous cord that encircled the common truncus. The ostium had three well developed cusps. There were two coronary orifices; the right coronary orifice was in the anterior sinus, and the left coronary orifice was in the left posterior sinus. The intima of the common trunk was smooth and whitish; there was no ridge or other evidence of a vestigial septum. The branches of the truncus, in their normal positions, were the coronary, the innominate, the left common carotid and the left subclavian arteries. On the descending portion of the arch, 1 cm. from the orifice of the subclavian artery, was the ductus arteriosus with a patent lumen 5 mm. in diameter. This vessel had a main stem 5 mm. long, which divided into two branches; one entered the hilus of the left lung, and the other extended to the hilus of the right lung. No other vessel was found emerging from the heart, nor the fibrous cord of an atretic vessel. The remainder of the branches of the thoracic and abdominal aorta appeared normal. The left atrium was comparatively small and was connected with the pulmonary veins from both lungs. The mitral valve had two normal-appearing leaflets. Its orifice was 3.2 cm. in circumference. The left ventricle had an inner circumference that measured up to 3 cm., and the distance from the mitral ring to the apex was 3.4 cm. Its wall was 6 mm. thick at the base of the anterior papillary muscle and 4 mm. thick at the apex. The weight of the heart with the attached common trunk and the descending thoracic aorta was 59.3 Gm.

Microscopically, bronchopneumonia, pulmonary edema and congestion, fatty hepatic change and cloudy swelling of the kidneys were observed.

## COMMENT

The anatomic features of this case were as follows:

1. There was only one large vessel at the base of the heart. This truncus straddled the interventricular septum and thus emerged from both ventricles, approximately two thirds from the right and one third from the left. Its orifice was guarded by three well developed cusps. The truncus gave off two coronary arteries and the systemic arteries in their normal positions.

2. The aorta and the pulmonary arteries were undifferentiated. It is generally held that the arch of the aorta and its branches, except

the right subclavian, develop from the left member of the fourth pair of aortic arches. The right and left pulmonary arteries develop from the sixth pair of aortic arches. Fusion of the paired spurs of the fourth and sixth aortic arches and their caudal extension form the aortic-pulmonary septum. In this case there was no ridge or septum in the wall of the truncus, indicating the absence of structures derived from the sixth arch. This type of deformity is classified as complete, to differentiate it and the partial type in which some remnant of the aortic-pulmonary septum remains.

3. The pulmonary circulation was supplied by a large vessel which branched from the truncus at the site of the ductus arteriosus. This is a most unusual site for the origin of the pulmonary arteries, and the literature contains a report of only 1 previous case (Hunter [3]). In other cases the pulmonary arteries have originated as two large branches from the wall of the common truncus some distance above its origin, or as a single vessel which divides, sending a branch to each lung. In the case of Graham and Montgomery [8] the pulmonary circulation was supplied by two small arteries arising from the truncus distal to the great vessels; apparently these were bronchial arteries. In Kettler's [9] case the truncus, immediately above the ostium, divided into a larger aortic branch and a smaller pulmonary branch.

4. The interventricular septal defect was in the upper membranous part of the septum. Varying degrees of defectiveness of the septum have been described. It may be rudimentary or absent. The dextroposition may be such that the ostium emerges more or less entirely from the right ventricle, with the blood entering it from the left through the defect. One would expect the interventricular defect to cause a loud systolic murmur to the left of the sternum, but none was recorded in this case.

5. There was a patent foramen ovale. In the Lev-Saphir [4] tabulation some cases are listed in which the auricular septum was almost or completely absent.

6. The right auriculoventricular valve had only two leaflets. In this respect the case is similar to that of Lev and Saphir.[4] They explained this on the basis that the bulbus was absorbed earlier in fetal life than the formation of the valves and the presence of the large truncus in the right ventricle at the time of the formation of the valves created current relationships similar to those at the mitral valve: The inflow areas of the right ventricle met at a very acute angle, so that development of a third leaflet was inhibited.

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8. Graham, S., and Montgomery, G. L.: J. Tech. Methods **81**:97, 1938; cited by Lev and Saphir.[4]

9. Kettler, L. H.: Virchows Arch. f. path. Anat. **304**:513, 1939.

SUMMARY

The case of truncus arteriosus communis persistens presented is the thirty-eighth to be recorded and the second in which the pulmonary arteries were branches of a patent ductus arteriosus. Death occurred from malnourishment and bronchopneumonia at the age of 6 months. Only 2 patients with this anomaly have been known to live to adult life: One died at the age of 16 and the other at 25.

There is no conclusive explanation for the anomaly. In the literature are the theories of Spitzer,[10] Humphreys [1] and Lev and Saphir.[4] The anomaly may be associated with abnormal torsion which results in failure or impairment of septal formation. In this case there was aplasia or complete early regression of sixth arch structures.

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10. Spitzer, A.: Virchows Arch. f. path. Anat. **243**:81, 1923; cited by Humphreys.[1]

# ATHEROSCLEROSIS AND ARTERIOSCLEROSIS IN DOGS FOLLOWING INGESTION OF CHOLESTEROL AND THIOURACIL

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SINCE Anitschkow [1] demonstrated in 1913 that lesions similar to those of human atherosclerosis develop in the arteries of rabbits fed large amounts of cholesterol, numerous investigators have attempted to produce experimental atherosclerosis by feeding cholesterol to other animals. However, these efforts have succeeded only with regard to chickens [2] and guinea pigs.[3] Attempts to produce atherosclerosis in dogs, cats and monkeys by cholesterol feeding have failed.[4] The cholesterol added to the normal diets of these animals has not caused hypercholesteremia comparable to that occurring in rabbits.

A previous report from this laboratory [5] showed that moderate hypercholesteremia (300 to 400 mg. of cholesterol per hundred cubic centimeters of serum) maintained for forty-four to fifty-six weeks by feeding egg yolk powder to dogs did not give rise to arterial lesions. However, these levels were much lower than those attained in rabbits. In a recent article Li and Freeman [6] reported that extreme hypercholesteremia, with cholesterol values as high as 1,700 mg. per hundred cubic centimeters of serum, could be maintained in dogs for periods up to eighteen weeks by feeding cholesterol with a diet high in fat and deficient in protein. When the protein was adequate, the increases in serum

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1. Anitschkow, N.: Beitr. z. path. Anat. u. z. allg. Path. **56**:379, 1913.
2. Dauber, D. V., and Katz, L. N.: Arch. Path. **34**:937, 1942.
3. Bailey, C. H.: Proc. Soc. Exper. Biol. & Med. **13**:60, 1915.
4. Anitschkow, N.: Verhandl. d. deutsch. path. Gesellsch. **20**:149, 1925. Pfleiderer, E.: Virchows Arch. f. path. Anat. **284**:154, 1932. Orio, L.: ibid. **269**:739, 1928. Wacher, L., and Huech, W.: Arch. f. exper. Path. u. Pharmakol. **74**:416, 1913. Kawamura, R.: Neue Beiträge zur Morphologie der Cholesterinsteatose, Jena, G. Fischer, 1927.
5. Steiner, A., and Domanski, B.: Am. J. M. Sc. **201**:820, 1941.
6. Li, T., and Freeman, S.: Am. J. Physiol. **145**:646, 1946.

cholesterol were only moderate. No atherosclerosis was observed in their dogs with high cholesterol levels.

It seems possible that in dogs and other omnivorous animals the mechanism for regulating cholesterol metabolism may continue to function effectively in spite of the ingestion of abnormal amounts of cholesterol. Production of hypercholesteremia may be dependent on our modifying this mechanism in some way. Many investigators have shown that the thyroid gland plays a part in the regulation of serum cholesterol levels.[7] Unpublished experiments demonstrated that after thyroidectomy the addition of cholesterol to the diet resulted in marked hypercholesteremia in dogs.[8] However, partial or complete removal of the parathyroid glands during the thyroidectomy made it difficult to maintain the dogs in a state of good nutrition.

In the investigation reported in this paper the thyroid activity of 4 dogs was modified by the administration of thiouracil [9] and the effect on the serum cholesterol levels and on the development of arterial lesions was studied.

## METHOD

Four adult mongrel dogs, 2 males and 2 females, weighing 20 to 53 pounds (9 to 24 kg.), were employed. In the beginning of the experiment the dogs were fed approximately 325 Gm. of a prepared food daily.[10] Their appetite for this diet was erratic; therefore, after the first six months, the diet was changed to approximately 200 Gm. of ground beef mixed with 125 Gm. of the prepared food. The experiment was divided into three periods: an initial control period of eight weeks, a thiouracil feeding period of eight weeks and a thiouracil-plus-cholesterol feeding period of forty-eight to fifty-six weeks. The dogs were fed 0.5 Gm. of thiouracil daily for the first month. This dose was increased to 0.8 Gm. during the second and third months, to 1.0 Gm. from the fourth through the ninth month and finally to 1.2 Gm. from the tenth month until the end of the experiment. The amount of thiouracil was not increased beyond 1.0 Gm. daily in dog 376. It was fed by placing 0.1 Gm. tablets as far back in the posterior part of the pharynx as possible and then holding the jaws of the dog tightly closed. In the early phase of the experiment the dogs would occasionally regurgitate the thiouracil. This difficulty was overcome by allowing them to eat soon after the feeding of the drug. The thiouracil dose was increased three times in the first nine months because the elevated serum cholesterol levels gradually fell toward normal. The effect of thiouracil on the general bodily state was especially pro-

7. (*a*) Luden, G.: J. Lab. & Clin. Med. **4**:849, 1918. (*b*) Epstein, A. A., and Lande, H.: Arch. Int. Med. **30**:563, 1922. (*c*) Hurxthal, L. M.: ibid. **51**: 22, 1933.

8. Steiner, A.: Unpublished data.

9. Thiouracil was supplied by Dr. B. W. Carey, Lederle Laboratories, Inc., Pearl River, N. Y.

10. Spratt's Meat Fibrine Dog Cakes. The ingredients are wheat flour and meat meal, cooked. An analysis shows: crude protein, 20 per cent; crude fat, 2 per cent; fiber, 1.5 per cent; carbohydrates, 60 per cent; moisture, 7 per cent; ash, 2.5 per cent.

nouncd during the last six to eight months of the study. This was evidenced by lethargy, inactivity, drowsiness and bouts of shivering. Basal metabolism determinations were not made.

Ten grams of crystalline cholesterol mixed in 40 cc. of cottonseed oil was added daily to the diet of 3 of the 4 dogs (368, 377 and 378) after the first two months of thiouracil feeding. The fourth dog, 376, was maintained on thiouracil without the cholesterol supplement for the duration of this study and thus served as a control animal. The amount of the diet actually ingested varied considerably during the term of the experiment. It is estimated that throughout the course of the experiment the dogs ate from one half to two thirds of their diet. The dogs were weighed weekly. At the end of the experimnt dog 368 had gained 7 pounds (3 Kg.) while the others had lost weight: dog 378, 9 pounds (4 Kg.); dog 376, 6 pounds (about 3 Kg.), and dog 377, 5 pounds (a little over 2 Kg.).

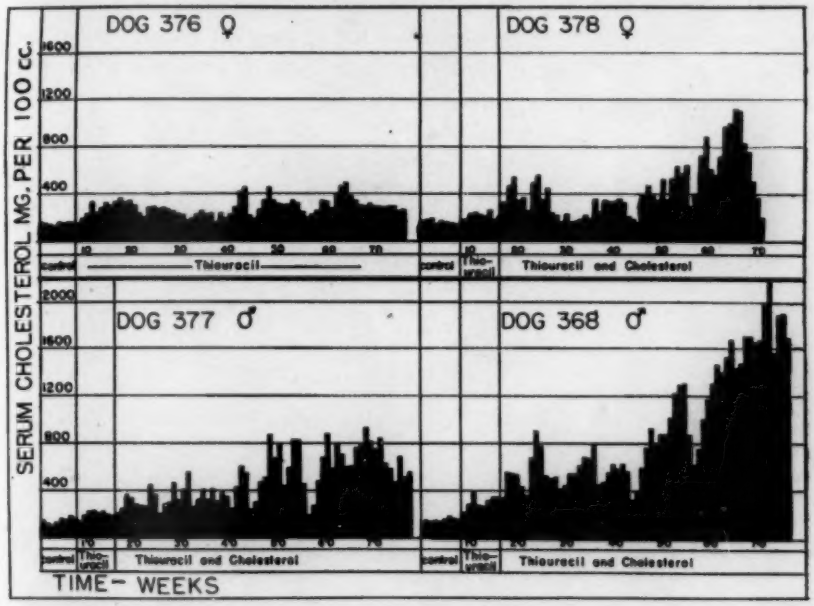


Fig. 1.—Levels of total serum cholesterol as determined at weekly intervals during the preliminary control period and during the periods when the dogs received thiouracil and thiouracil plus cholesterol.

Because of the refusal of dog 378 to eat the ration, the addition of the cholesterol in oil was discontinued between the twenty-fourth and thirty-first weeks and between the thirty-ninth and forty-second weeks. The total cholestrol feeding period of this animal was twelve months, while with the other 2 dogs, 368 and 377, the period was fourteen months. Serum cholesterol determinations were made weekly by a modification of the Schoenheimer-Sperry method.[11] Complete blood counts were made at bimonthly intervals.

At the end of the experiment the dogs were killed by exsanguination under pentobarbital sodium anesthesia.

11. Schoenheimer, R., and Sperry, W. M.: J. Biol. Chem. **106**:745, 1934.

RESULTS

The serum cholesterol values of each dog are shown graphically in figure 1. The ranges of the serum cholesterol values for each period of the experiment, together with the average values, are summarized in the table. It can be seen that feeding thiouracil alone produced an increase of serum cholesterol. This was followed by a much greater increase when cholesterol in cottonseed oil was added to the diet. As can be seen from figure 1, the level fluctuated considerably from week to week. Abrupt decreases in serum cholesterol always followed a decrease in cholesterol intake. This is especially apparent in the two periods during which cholesterol was not fed to dog 378 and in the period following the fiftieth week when all the dogs ate poorly. During the experiment the ratio between free and esterified cholesterol in the serum remained unchanged, approximately 1 to 2, even when the total cholesterol content of the serum was at its highest.

*Serum Cholesterol Values*

| Dog | Control Period | | Thiouracil | | Thiouracil and Cholesterol | |
|---|---|---|---|---|---|---|
| | Range, Mg. per 100 Cc. | Months | Range, Mg. per 100 Cc. | Months | Range, Mg. per 100 Cc. | Months |
| 368 (male)..... | 141-191 (av. 157) | 2 | 221-348 (av. 308) | 2 | 408-2,176 (av. 979) | 14 |
| 377 (male)..... | 108-186 (av. 147) | 2 | 192-252 (av. 216) | 2 | 196- 932 (av. 534) | 14 |
| 378 (female)..... | 139-192 (av. 162) | 2 | 160-333 (av. 208) | 4 | 208-1,134 (av. 500) | 12 |
| 376 (female)..... | 136-158 (av. 152) | 2 | 149-490 (av. 284) | 16 | ..... | .. |

The blood counts of the 4 dogs remained essentially unchanged. Agranulocytosis did not occur.

The 4 animals were examined post mortem by Dr. Joseph Victor.

*Dog 368 (27.7 Kg., male).*—Gross changes were observed in the aorta and its branches and in the heart, the liver, the gallbladder and extrahepatic bile ducts, the kidneys, the thyroid gland, the stomach and the small intestine. Although the thoracic portion of the aorta was clear and smooth, elevated cream-colored and gray plaques appeared in the abdominal portion below the diaphragm and increased in size and number toward and beyond the bifurcation of the iliac arteries. The plaques were conspicuous about the orifices of the branches (fig. 2). Similar changes were evident in the coronary, pulmonary, thyroid, celiac, mesenteric, renal, iliac and femoral arteries. The lesions in the coronary arteries and their branches measured up to 2 cm. in length and seemed to fill the lumens. The thyroid arteries were converted into straight, rigid, thickened vessels about 1.5 mm. in diameter. Calcified plaques were present in both iliac arteries. No lesions were found in the cerebral, carotid, retinal or splenic arteries.

Although only moderate amounts of fat were seen in the subcutaneous, mesenteric, omental and retroperitoneal tissues, fatty deposits were prominent in the heart, the liver, the gallbladder, the bile ducts and the kidneys. The heart weighed 171 Gm. and its muscle, especially that of the right ventricle, was mottled with yellow streaks. The liver weighed 813 Gm. and was yellow and greasy. The gallbladder and the bile ducts had a velvety mucosa with glistening, bright

Fig. 2.—Abdominal aorta, iliac artery and femoral artery of dog 368. The aorta shows arteriosclerotic plaques at the orifices of branches; the iliac and femoral arteries show arteriosclerosis. The dark plaques are calcified.

yellow villi, which in places had coalesced to form bright golden nodules measuring up to 2 mm. in diameter. The kidneys weighed 119 Gm. and had dark brown cortices with "hairlike" yellow streaks in the intermediate zones. The adrenal glands weighed 2.1 Gm. Beginning in the cardia of the stomach and extending throughout the small intestine to the ileocecal valve, the muscularis was brown. The mucosa, in contrast, was creamy white. The colon was unaltered. The thyroid gland was greatly enlarged, the combined weight of the lobes being 9 Gm.

On microscopic examination, features characteristic of arteriosclerosis were apparent in the lesions of the abdominal portion of the aorta and in the coronary, iliac, femoral and thyroid arteries. In all these vessels the intima showed foam cell infiltration, which in many cases penetrated the inner part of the media. The internal elastica was thickened, reduplicated and occasionally fragmented. Elastic fibrils were seen in the thickened intima. Anisotropic cholesterol crystals were present within the foam cells. The abdominal portion of the aorta had, in addition, areas of intimal hyalinization (fig. 3 *A*). The main coronary and thyroid arteries showed layers of fibrous connective tissue between the intimal foam cells (figs. 3 *B* and 4 *A*). Several calcified intimal plaques which extended into the media were present in the internal iliac arteries.

Examination of organs showed atherosclerotic lesions in branches of the coronary, pancreatic (fig. 4 *B*), renal, testicular and mesenteric arteries. These lesions were characterized by intimal collections of foam cells without fibrosis or hyalinization.

The pulmonary arteries had intimal changes which differed considerably from those of other arteries. These lesions were considered to be endarteritis obliterans.

Histologic changes were present in many other tissues. Myocardial fibrosis was found in small areas near the thickened coronary arteries. Excessive quantities of fat were observed in fat cells between myocardial fibers and within epithelial cells of the liver, Henle's loops of the kidneys, intrahepatic and extrahepatic bile ducts, the gallbladder and the mucosa of the small intestine. Ceroid pigment, which was brilliant red in Ziehl-Neelsen stains, occurred within histiocytes of the liver, the epididymis, lymph nodes, the spleen, the stomach and the small intestine as well as within smooth muscle cells of the cardia, the pyloris and the small intestine. In the distal convoluted tubules of the kidney there were great quantities of amorphous globules of brown pigment, which was orange-colored in Ziehl-Neelsen preparations. The thyroid gland was hypertrophied and hyperplastic, with papillary infoldings of the acini lined by cuboidal and columnar epithelium up to four cells thick. Colloid was often absent from the acinous spaces. The testes showed no spermatogenesis, the tubules being lined by swollen Sertoli cells. Many of the chromophobe cells of the anterior lobe of the pituitary gland had foamy cytoplasm, and some contained homogeneous eosinophilic spherical bodies about 15 to 20 microns in diameter.

*Dog 377 (9.1 Kg., male).*—Gross changes were seen in the abdominal portion of the aorta and its branches and in the heart, the liver, the gallbladder, the bile ducts, the kidneys, the thyroid gland and the small intestine. Cream-colored intimal plaques were found in the aorta, beginning at the diaphragm and increasing in number and size peripherally. Similar lesions were also observed in the coronary, celiac, renal, mesenteric, iliac and thyroid arteries. The lesions were less severe than those in dog 368. No calcification was noted. Fatty changes were seen in the heart and the liver. The heart weighed 104 Gm., and there was yellow mottling of the myocardium. The liver weighed 478 Gm. and was yellow, fat and firm. The gallbladder and the bile ducts had a velvety mucosa,

which was tinted with glistening golden-tipped villi. The kidneys weighed 54 Gm. and had dark brown cortices. The adrenal glands weighed 1.8 Gm. and had wide cortical zones. The jejunum had tan-colored muscularis, while the mucosa of the entire small intestine was creamy white. The thyroid gland weighed 8.5 Gm.

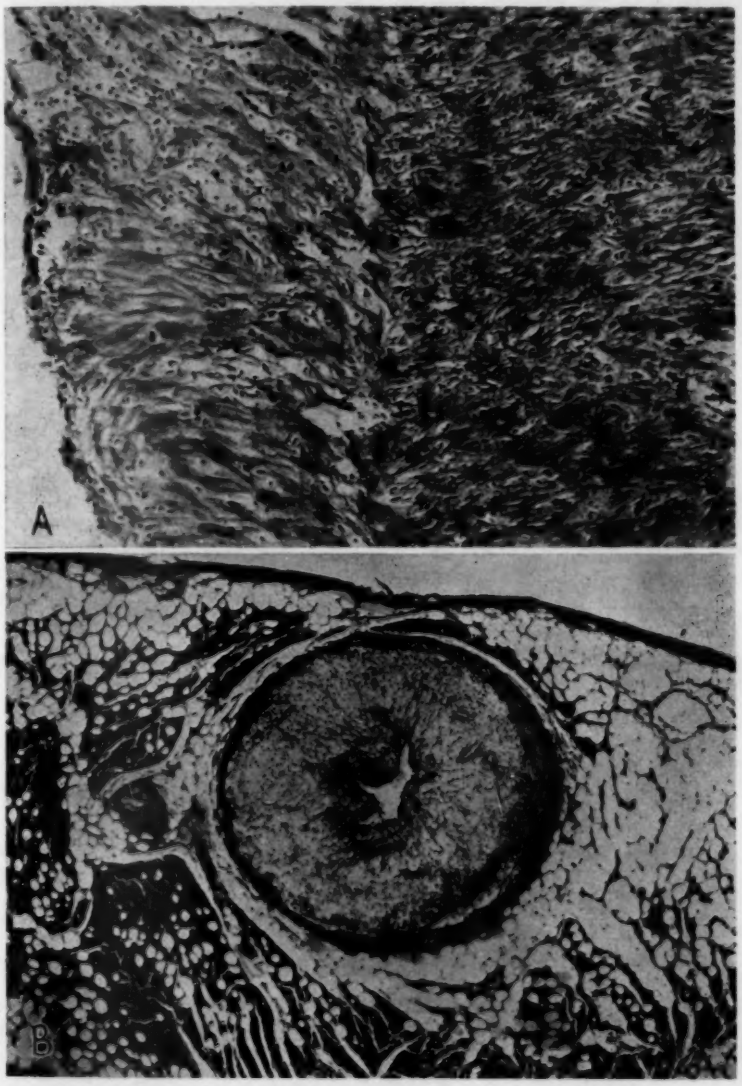


Fig. 3.—*A*, photomicrograph of abdominal aorta. The intimal plaque consists of hyalinized connective tissue, lymphoid cells and mononuclear cells with foamy cytoplasm. The mononuclear cells also occur in the inner part of the media. Giemsa stain. × 100.

*B*, photomicrograph of the coronary artery and myocardium. The intima of the artery is thickened by fibrous connective tissue and foam cells. Most of the media is replaced by these cells. Recanalization of the plaque has occurred. Many fat cells separate the myocardial fibers. Masson's trichrome stain. × 50.

Microscopically, the arterial lesions consisted of intimal deposits of fat and infiltrating foam cells without hyalinization or fibrosis. The foam cell infiltration penetrated the inner part of the media in many lesions. Changes in the smaller branches of the arteries were seen only in the thyroid gland. Fatty deposits were present in the organs. The fatty changes were similar in character and

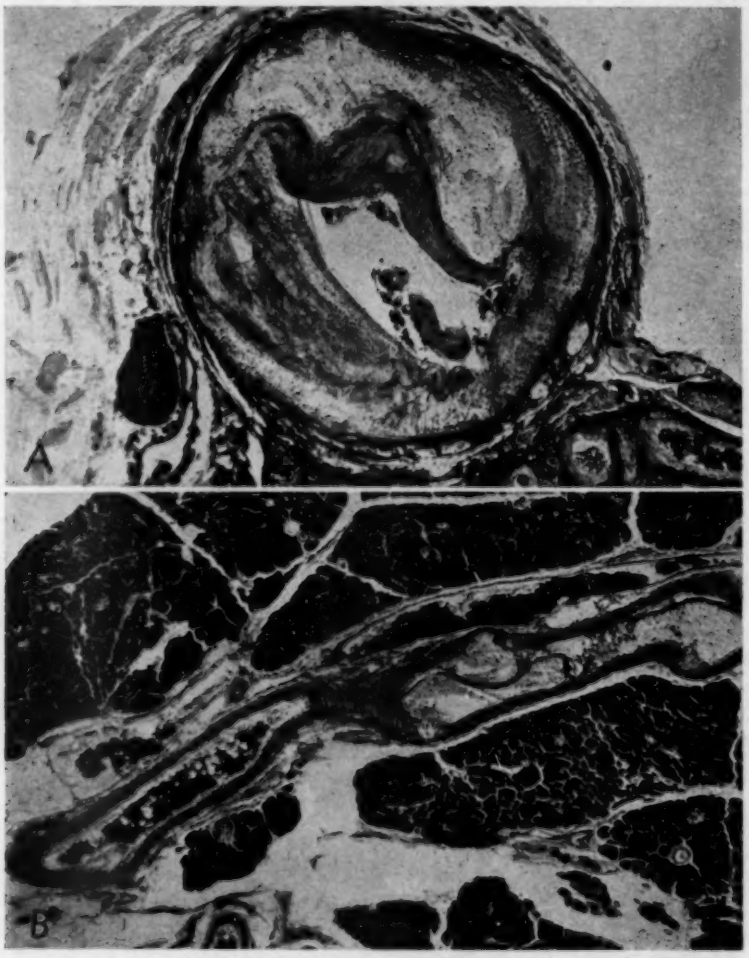


Fig. 4.—*A*, photomicrograph of the thyroid artery. Note the intimal fibrosis and foam cell infiltration. The media is occupied by foam cells and fat spaces. Masson's trichrome stain. × 50.

*B*, photomicrograph of the pancreatic artery. The thickening of the intima is due to foam cells. Masson's trichrome stain. × 50.

distribution to those described for dog 368 but were less extensive. Ceroid was found in the smooth muscle cells and histiocytes of the jejunum. Excessive quantities of brown pigment which was not acid fast occurred in the renal distal convoluted tubules. Hyperplasia of the thyroid gland resembled that seen in dog 368. Spermatogenesis was active.

*Dog 378 (9.5 Kg., female).*—There were changes in the thyroid gland, the liver, the gallbladder and the kidneys. The aorta and its large branches were unaltered. The hypertrophy of the thyroid gland was extraordinary, the combined weight of the two lobes being 13.0 Gm. The liver weighed 490 Gm. It was yellow, fat and greasy and had a finely granular capsule. The mucosa of the gallbladder was velvety with glistening golden yellow villi, many of which coalesced to form xanthomatous masses measuring up to 3 mm. in diameter. The extrahepatic bile ducts had mucosa resembling that of the gallbladder. The renal cortices were dark brown with scattered gray flecks about 0.5 mm. in diameter. Hairlike yellow streaks were present in the intermediate zones. Organ weights in grams were: heart, 64.0; spleen, 26.0; kidneys, 45.0; adrenal glands, 2.0.

Microscopic evidence of vascular lesions was found only in the arteries of the thyroid gland and the ovaries. The essential change was atherosclerosis with subendothelial deposits of enormous foam cells. In the ovarian arteries the atherosclerosis was associated with thrombosis caused by blood elements and recanalization by proliferating endothelium-lined capillaries. Other noteworthy tissue alterations were present. Extraordinary deposits of fat were found in the epithelial cells of the liver, the intrahepatic bile ducts, the gallbladder, the renal loops of Henle and between the cardiac muscle fibers. Intense pigmentation with a brown amorphous granular material occurred in the epithelial cells of the renal distal convoluted tubules. The pigment had an orange color with Ziehl-Neelsen stain. Large masses of acid-fast ceroid pigment occurred in the histiocytes of the liver, the ovarian stroma, the uterine endometrium, the hypophysial pars nervosa and the lymph nodes. Thyroid hyperplasia and hypertrophy were extreme. Colloid was often absent from the acinous spaces. The anterior lobe of the pituitary gland had many swollen cells about three times the usual diameter, with ground glass, foamy or partly hyalinized cytoplasm.

*Dog 376 Thiouracil Control (11.4 Kg., female).*—The only changes were enlargement of the thyroid gland and brown pigmentation of the renal cortex and the muscle of the jejunum. The aorta and its branches were unaltered. On microscopic examination hypertrophy and hyperplasia of the thyroid gland were apparent. A pigment having the characteristics of ceroid was present in the jejunal muscle fibers and in the histiocytes between the longitudinal and circular layers of muscle. Similar pigment occurred in a few histiocytes of ovarian and endometrial stroma. The brown color of the renal cortex was due to the presence of small amounts of a pigment similar to that found in the other dogs. The blood vessels were normal. Weights of organs in grams follow: heart, 98; spleen, 20.6; liver, 280; adrenal glands, 1.5; kidneys, 35.1; thyroid gland, 5.1.

## COMMENT

Hypercholesteremia was produced in dogs and maintained for long periods by feeding cholesterol after the function of the thyroid gland had been modified by administration of thiouracil. A daily dose of from 0.5 to 1.2 Gm. of thiouracil without cholesterol produced increases of from 50 to 140 mg. per hundred cubic centimeters in the average serum cholesterol content. This increase is of the same magnitude as that which followed thyroidectomy.[7c] The addition of 10 Gm. of cholesterol and 40 cc. of cottonseed oil to the daily diet of 3 dogs receiving thiouracil resulted in extreme hypercholesteremia. The ele-

vation of level over the base line reached a maximum of 770, 980 and 2,000 mg. per hundred cubic centimeters in the 3 dogs. Maintenance of the high level of serum cholesterol depended on both the cholesterol intake and the dose of thiouracil. Whenever the dogs ate poorly, thus reducing the cholesterol intake, the serum levels fell. The dose of thiouracil was increased at three different times during the experiment. In general, on these occasions further increases of the cholesteremia occurred in the cholesterol-fed dogs but did not occur in the control dog receiving only thiouracil.

Arterial lesions were produced in the 3 dogs receiving cholesterol. These lesions were considered to be those of atherosclerosis when the arterial intima showed foam cell infiltration without fibrosis, hyalinization or calcification. They were considered to be those of arteriosclerosis when one or more of these features were present together with foam cell infiltration. The extent and the severity of the arterial lesions paralleled the duration and the degree of the hypercholesteremia in these dogs. Dog 376, whose serum cholesterol level never exceeded 500 mg. per hundred cubic centimeters, had no vascular lesions. Dog 378, whose serum cholesterol level was over 500 mg. per hundred cubic centimeters for ten weeks, had atherosclerotic lesions in the ovarian and thyroid arteries only. Dog 377, with levels in excess of 500 mg. per hundred cubic centimeters for twenty-seven weeks, had atherosclerosis of the abdominal portion of the aorta and its branches and of the coronary and thyroid arteries. Dog 368 had levels exceeding 500 mg. per hundred cubic centimeters for fifty-two weeks and exceeding 1,000 mg. for twenty-three weeks; in this animal atherosclerotic and arteriosclerotic lesions were widely distributed. The 3 dogs receiving cholesterol had abnormal fat deposits in the heart, the liver, the kidneys and the adrenal glands.

Hyperplasia and hypertrophy of the thyroid gland were seen in all the dogs. The changes resembled those described as resulting from thiouracil administration in other species.[12] As might be expected the changes were more extreme in the thyroid glands of the smaller dogs since the dose of thiouracil was not adjusted to body weight. Thus dogs 377 and 378, weighing 11.4 Kg. and 9.5 Kg., and control dog 376, weighing 11.4 Kg., showed much more thyroid hypertrophy than did dog 368, which weighed 27.7 Kg.

Ceroid pigment was observed in certain tissues of the 4 dogs fed thiouracil. Since the extent and the severity of the pigmentation were greatest in dog 368 and least in control dog 376, the phenomenon paralleled the hypercholesteremia rather than the hyperplasia of the thyroid gland. The distribution of the pigment, which was most abun-

12. MacKenzie, C. G., and MacKenzie, J. B.: Endocrinology **32**:185, 1943.

dant in smooth muscle cells of the small intestine, resembled that observed in human beings with sprue [13] and in dogs with bile fistula.[14] Although ceroid pigmentation may be influenced by dietary vitamin E,[15] no evidence of vitamin E deficiency was found.

Progress in the study of arteriosclerosis is largely dependent on the ability to reproduce the disease in experimental animals. Because of the nature of the lesions, it is difficult to follow the development of the disease in human beings. Up to the present time lesions similar to those seen in human arteriosclerosis have been produced most successfully in the rabbit. In this species hypercholesteremia produced by feeding cholesterol is consistently followed by the development of arterial lesions. Although, in many respects these lesions resemble those seen in man,[16] Duff and other investigators [17] have emphasized certain differences. The distribution of the lesions differs from that most frequently seen in human atherosclerosis and arteriosclerosis. In rabbits the lesions are most concentrated in the arch and the thoracic portion of the aorta. In man the lesions occur mainly in the abdominal portion of the aorta and its branches. Inasmuch as similar lesions have not previously been reported to have been produced in omnivorous mammals such as the dog, the cat or the monkey, the suggestion has been made that the lesions in the rabbit represent the response of a herbivorous animal to a substance not normally present in its diet and that they have no relationship to the lesions occurring in man.

However, arterial lesions have now been shown to follow sustained hypercholesteremia in dogs. If the differences in the normal serum cholesterol levels and in the life spans of the two species are taken into consideration, the conditions necessary for the production of the arterial lesions are similar in rabbits and dogs. Although in the 2 dogs in which gross arterial lesions developed the serum cholesterol level was higher than that required to produce lesions in rabbits, the percentage increase in level was similar. Lesions appear in rabbits after the serum cholesterol has been maintained at a level from three to ten times the normal for a period of from six to ten weeks. Gross lesions were found in the dogs after the serum cholesterol had been maintained at levels from three to ten times the normal for dogs for at least twenty-seven weeks.

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13. Pappenheimer, A. M., and Victor, J.: Am. J. Path. **22**:395, 1946.

14. Whipple, G. H., and Hooper, C. W.: Am. J. Physiol. **43**:275, 1917.

15. Martin, A. J. P., and Moore, T.: Chem. & Indust. **57**:973, 1938.

16. Anitschkow, N., in Cowdry, E. V.: Arteriosclerosis, New York, The Macmillan Company, 1933. Leary, T.: Arch. Path. **21**:459, 1936; **32**:507, 1941.

17. Duff, L.: Arch. Path. **20**:81 and 259, 1935. Aschoff, L.: Brit. M. J. **2**:1131, 1932.

It is possible that the thyroid involvement in these dogs influenced the development of the arterial lesions in some way not connected with the hypercholesteremia. However, since no arterial lesions were found in the control dog, which had similar thyroid involvement without marked hypercholesteremia, the cholesterol level seems to be the decisive factor.

The distribution of the arterial lesions in these dogs is different from that observed in rabbits and is strikingly similar to that found in human arteriosclerosis. In morphologic characteristics the lesions vary from atherosclerotic lesions similar to those seen in rabbits to lesions with fibrosis, hyalinization and calcification similar to those seen in human material.

It is probable that the fundamental disease process is the same in dogs and rabbits and that the differences in the distribution and the morphologic character of the arterial lesions are due to some unidentified anatomic factor. The ability of the dog to metabolize considerable quantities of cholesterol increased the difficulty of maintaining a condition of hypercholesteremia but did not prevent the development of arterial lesions after the hypercholesteremia was established.

Although arteriosclerosis of man is too protean a disease to have a single cause, the results reported here justify the belief that at least in the cases in which arteriosclerosis follows hypercholesteremia the disease is similar to that produced experimentally in animals. It seems important, therefore, to continue studies of factors which may modify the lesions following hypercholesteremia in experimental animals.

## SUMMARY

Arterial lesions similar in distribution and morphologic character to those seen in human atherosclerosis and arteriosclerosis were found in dogs following prolonged hypercholesteremia. The high serum cholesterol levels were produced by feeding 10 Gm. of cholesterol in 40 cc. of cottonseed oil daily to dogs whose thyroid function was modified by administration of thiouracil.

# FURTHER EVIDENCE FOR SUCCESSIVE STAGES IN THE FORMATION OF NEOPLASMS

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ONE OF the most significant findings in the field of cancer research is the observation that carcinogenesis can be augmented or retarded by certain extrinsic or intrinsic agents.[1] In this field investigations have a far greater importance than the mere search for agents with cocarcinogenic or anticarcinogenic properties, since such studies have provided some fundamental concepts about carcinogenesis itself. While the work is incomplete, two corollary conclusions concerning this process appear justified at this time: First, cancer formation occurs not as a continuous single process but rather as a series of biologic changes; second, certain forces other than those actually involved in the genesis of the tumor cell are necessary for the formation of grossly perceptible neoplasms.

Although these two conclusions have been expressed previously,[2] there is no unanimity of opinion as to the exact role of the various forces necessary for tumor formation or as to the sequence of their action. One theory holds that the carcinogen first induces a neoplastic cell or cells from normal tissue and then stimulates the proliferation of such cells. This proposal emphasizes the difference in the genesis and the growth of neoplasms, and in various forms it has received the support of Berenblum,[1a] Kline and Rusch [2a] and Friedewald and Rous.[1b] A second hypothesis, advanced by Simpson and Cramer,[3] proposes that methylcholanthrene is a sensitizing agent, itself noncarcinogenic, that prepares the cells for subsequent carcinogenic action by the metabolic

From the McArdle Memorial Laboratory, University of Wisconsin Medical School.

This investigation was aided by the Jonathan Bowman Fund for Cancer Research.

1. (*a*) Berenblum, I.: Arch. Path. **38**:233, 1944. (*b*) Friedewald, W. F., and Rous, P.: J. Exper. Med. **80**:101, 1944. (*c*) Kreyberg, L.: Acta path. et microbiol. Scandinav. (supp.) **37**: 317, 1938. (*d*) Rusch, H. P.: Physiol. Rev. **24**:177, 1944.

2. (*a*) Kline, B. E., and Rusch, H. P.: Cancer Research **4**:762, 1944. (*b*) MacKenzie, I., and Rous, P.: J. Exper. Med. **73**:391, 1941. (*c*) Rous, P., and Kidd, J. G.: ibid. **73**:365, 1941. (*d*) Tannenbaum, A.: Cancer Research **4**:678, 1944. (*e*) Berenblum.[1a] (*f*) Friedewald and Rous.[1b] (*g*) Rusch.[1d]

3. Simpson, W. L., and Cramer, W.: Cancer Research **5**:5, 1945.

| Group | Treatment * | | Effectual Total† | Cumulative Tumor Count at Given Number of Months After the First Application of the Carcinogen | | | | | | | | | | | | | | | Number of Mice Tumor Free and Alive at Nine Mo. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 3 | | 4 | | 5 | | 6 | | 7 | | | 8 | | 9 | | | |
| | First Period, 4 Months | Second Period, 3 Months | | P§ | Ca§ | P | Ca | P | Ca | P | Ca | P | Ca | Percentage of Mice with Tumors‡ | P | Ca | P | Ca | Percentage of Mice with Tumors‡ | |
| 1 | Methylcholanthrene in benzyl alcohol | Same as first period | 38 | 2 | 0 | 15 | 0 | 29 | 0 | 27 | 8 | 16 | 22 | 100 | 12 | 26 | 4 | 34 | 100 | 0 |
| 2 | Methylcholanthrene in wool fat | Same as first period | 40 | 0 | 0 | 0 | 0 | 2 | 0 | 3 | 0 | 9 | 1 | 25 | 14 | 5 | 18 | 7 | 62 | 12 |
| 3 | Methylcholanthrene in wool fat | Methylcholanthrene in benzyl alcohol | 40 | 0 | 0 | 0 | 0 | 4 | 0 | 18 | 0 | 28 | 9 | 92 | 20 | 18 | 14 | 24 | 95 | 0 |
| 4 | Methylcholanthrene in wool fat | Croton oil in benzyl alcohol | 40 | 0 | 0 | 1 | 0 | 7 | 0 | 13 | 2 | 22 | 3 | 62 | 21 | 7 | 19 | 7 | 64 | 7 |
| 5 | Methylcholanthrene + croton oil in wool fat | Same as first period | 40 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 10 | 0 | 25 | 15 | 3 | 18 | 7 | 62 | 14 |
| 6 | Methylcholanthrene in benzyl alcohol | Methylcholanthrene in wool fat | 34 | 3 | 0 | 18 | 0 | 26 | 1 | 22 | 7 | 18 | 14 | 94 | 11 | 17 | 6 | 20 | 77 | 0 |

* Methylcholanthrene was used as a 0.3 per cent and croton oil as a 1 per cent solution in all cases.

† This total was the number of animals alive at the time the first tumor appeared.

§ P stands for papilloma; Ca, for carcinoma.

‡ Percentage of mice with tumors is based on the effectual total. Both those with papilloma and those with carcinoma are included.

derivatives of the hydrocarbon. Both theories are based on evidence that carcinogenic hydrocarbons possess biologic properties other than those involved in the genesis of the tumor cells. The experiments reported in the following pages were designed to obtain further information concerning these various properties and to present additional evidence that supports the existence of well defined stages in the development of neoplasms.

## MATERIALS AND PROCEDURE

A series of 240 ABC young adult albino mice of both sexes were divided into six groups of 40 each. The sexes were separated and were kept in groups of 20 in metal box cages on shavings, with dog biscuit and water available at all times. The experiment was divided into two periods: The initial course of treatment was continued for four months and was followed by a second of three months' duration. For the second period the treatment was changed in some of the groups. Initially the mice were painted twice weekly with a solution of 0.3 per cent methylcholanthrene in benzyl alcohol, in wool fat (anhydrous) or in wool fat containing 1 per cent croton oil. The various preparations were applied to the skin of the interscapular area with a camel's hair brush. Because of the pasty character of the mixtures that contained wool fat there was some doubt as to whether the same amount of methylcholanthrene had contact with the skin as when benzyl alcohol was the solvent. To obviate this difficulty, the hair was clipped from the painted area every two weeks. In the second period, one of the groups (no. 4) was painted with a cocarcinogenic mixture consisting of 1 per cent croton oil in benzyl alcohol, and another group (no. 5) received a mixture of 0.3 per cent methylcholanthrene and 1 per cent croton oil in wool fat. The remaining groups continued to receive methylcholanthrene, either in benzyl alcohol or in wool fat. The exact treatment given in both periods is shown with the results in the table. The mice were examined carefully at weekly intervals for the appearance of tumors and were kept an additional two months beyond the last application of the carcinogen in order that latent effects might be observed. The growth of the neoplasms was closely followed, and mice were removed from the experiment only after the tumors had attained a size sufficient to impair their health.

## RESULTS

The rate at which tumors appeared in the various groups is shown in the table. Since no striking difference in the incidence of tumors in the sexes was found, the numbers observed in the two sexes are not listed separately. When a solution of methylcholanthrene in benzyl alcohol was used, tumor formation was rapid, and at the end of the fourth month tumors (papilloma) were observed in 15 mice in group 1, and all of the mice in this group had tumors after the seventh month. In striking contrast to these results were those obtained when the carcinogen was dissolved in wool fat; no mice had tumors at four months and only 10 had them at seven months, but the incidence slowly increased to 62 per cent during the next two months (group 2). This is a higher incidence than that reported by Simpson and Cramer,[3] but the mice in the present series received a greater total amount of

carcinogen over a longer period. Besides the decrease in incidence of the tumors it is also of interest that only 7 mice with carcinoma were found in the group that received the carcinogen in wool fat, in contrast to 34 in the control group. It is obvious from this experiment that wool fat greatly retards but does not completely prevent tumor formation.

In order to obtain further information concerning the mode of action of wool fat and of methylcholanthrene, the latter was applied in different solvents at various periods. In one group the carcinogen in wool fat was painted on the skin the first four months, followed by a three month period during which the hydrocarbon was applied in a solution of benzyl alcohol. In none of the mice in this group did perceptible tumors develop during the initial four months of treatment, but neoplasms occurred rapidly in this group soon after the hydrocarbon–benzyl alcohol mixture was used, and by the end of the second period 92 per cent of the mice had tumors (group 3). There are at least two explanations for such results: Methylcholanthrene might have induced the formation of tumor cells following its application in wool fat but failed to stimulate such cells to proliferate because of some "neutralizing" or inhibiting effect of the wool fat. The growth of such "tumor rests" could then occur following the subsequent application of the carcinogen in the absence of wool fat. A second explanation is that proposed by Simpson and Cramer [3]; i. e., wool fat retarded the breakdown of methylcholanthrene, and the unaltered hydrocarbon acted merely as a sensitizing agent during the first period, thus preparing the skin for subsequent action of the metabolic derivatives of the carcinogen. If the former explanation is correct, it should be possible to evoke tumors after the initial carcinogenic treatment by the application of a non-carcinogenic irritant such as croton oil, whereas such a nonspecific irritant would not be expected to call forth tumors if the suggestion of Simpson and Cramer is valid. Group 4 was designed to test this point and differed from group 3 only in that a 1 per cent solution of croton oil was substituted for the methylcholanthrene in the second period. The influence of croton oil was similar to, but not as pronounced as, that obtained with the hydrocarbon. Tumor formation was accelerated following the application of the irritant and at seven months 62 per cent of the mice had tumors (group 4) compared with an incidence of 25 per cent in group 2, in which the mice had received methylcholanthrene dissolved in wool fat for the entire seven months. The cocarcinogenic effect of croton oil was largely confined to the period during which it was applied, and few new tumors were evoked after the cessation of treatments at the end of seven months. Thus the incidence of neoplasms rose to 70 per cent at the end of eight months, but during the next month the tumors (papilloma) in 2 mice regressed,

giving a final tumor incidence of 64 per cent at the end of the experiment. Methylcholanthrene, on the other hand, not only stimulated the formation of neoplasms already present but was also responsible for the genesis of new tumors when it was applied during the second period (group 3).

It is possible that the anticarcinogenic effect of wool fat is due to its ability to neutralize the "irritating" influence of methylcholanthrene and croton oil. In order to test this idea the mice of group 5 were painted for seven months with a solution of wool fat containing both methylcholanthrene and croton oil. In the absence of wool fat this combination of carcinogen and cocarcinogen is known to accelerate the induction of tumors.[4] The cocarcinogenic influence of croton oil was completely nullified in this experiment, and the results are perfect checks of those obtained in group 2, in which croton oil was absent. The inhibiting effect of wool fat may also be due to its physical characteristics rather than to any more subtle neutralizing powers. Its pasty consistency might permit only small amounts of the dissolved hydrocarbon to obtain contact with the surface of the skin and this in effect would result in the application of subcarcinogenic doses, which are known to induce similar changes.[2a]

To determine whether wool fat can inhibit the neoplastic process, once this has been initiated, a sixth group of mice were painted for the first four months with a solution of methylcholanthrene in benzyl alcohol, after which the hydrocarbon was applied to the skin in a solution of wool fat. Eighteen mice of this group had tumors before application of the wool fat–hydrocarbon mixture was started, and tumors continued to form rapidly thereafter even in the presence of the wool fat; 94 per cent of the mice had tumors at the end of seven months. However, the percentage of mice with cancers was slightly less than was found in the group that received the carcinogen in the absence of wool fat (group 1). Furthermore, a considerable number of tumors (papilloma) in group 6 regressed during the last two months of the experiment, and at the end of the ninth month the incidence of tumors was reduced to 77 per cent. It is possible that the initial period of treatment with the carcinogen was too long, and a greater differential between the results of group 6 and its control (group 1) could have been demonstrated if the application of wool fat had been started at the end of the third month. At all events it appears that wool fat is capable of neutralizing or inhibiting the properties of either carcinogen or cocarcinogen that are responsible for the proliferation of neoplastic tissue.

## COMMENT

Although the carcinogenic process has never been regarded as a simple one, recent investigations have indicated even greater complexities

4. Bereblum, I.: (*a*) Cancer Research **1**:44, 1941; (*b*) **1**:807, 1941.

than were previously suspected. Cancer formation appears not to occur as a continuous single process but rather as a series of biologic changes. Furthermore, there are definite indications that carcinogenic hydrocarbons are active only because of several distinct biologic properties, and neoplasms seem to develop only as the result of the proper sequential summation of these properties. That more than one quality of a carcinogen is involved in the formation of tumors gains support from the fact that some characteristics of hydrocarbons may be masked and others simulated by certain compounds. For example, the observation that an inhibiting effect is exerted on the carcinogenic activity of certain hydrocarbons by wool fat and by liquid petrolatum has been well established.[5] These anticarcinogens appear to neutralize or to mask the irritating effect of the hydrocarbons without affecting their ability to induce neoplastic cells since noncarcinogenic chemical or physical irritants quickly call forth neoplasms in tumor-free skin which had previously been treated with the hydrocarbons dissolved in wool fat or liquid petrolatum.[5] When wool fat was used as a solvent for methylcholanthrene, it largely abolished the irritating effects of the hydrocarbon on the skin, and epilation, destruction of sebaceous glands and epidermal hyperplasia were all minimal.[3] Such data suggest at least two biologic properties of carcinogenic hydrocarbons which are essential for the development of tumors: the ability to induce neoplastic cells and the ability to stimulate these cells to proliferative activity. The factor responsible for the genesis of the tumor is relatively bland and has not been duplicated to our knowledge with noncarcinogenic substitutes, while the property that causes cellular multiplication is due to a nonspecific irritant of the carcinogen and can be reproduced by other agents.[6]

The present experiments provide further evidence in favor of the concept that cancer formation results from a sequence of biologic changes. As a working hypothesis, the three periods listed in an earlier communication [2a] will be considered in light of the more recent findings:

1. *Period of Induction.*—This stage has also been referred to as the period of preparation, latency, initiation or preneoplasia.[7] Since some arbitrary limitations must be defined, this phase should include only the period of genesis of the neoplastic cell or cells from normal tissue, and it should not be confused with the multiplication of these cells.

Although any concept of carcinogenesis must include a period covering the genesis of the neoplastic cell, the exact sequence of this event in the process has not been demonstrated. Certainly it occurs

5. Friedewald and Rous.[1b] Simpson and Cramer.[3]

6. (*a*) Pullinger, B. D.: J. Path. & Bact. **55**:301, 1943. (*b*) Berenblum.[1a] (*c*) Friedewald and Rous.[1b] (*d*) Kline and Rusch.[2a] (*e*) Rusch.[1d]

7. Berenblum.[4b] Tannenbaum.[2d]

early, but in certain types of cancer it may be preceded by a period of preneoplasia during which tissues become biased toward forming neoplastic cells. In certain circumstances such a preliminary phase seems to be essential for the subsequent genesis of tumors. For example, certain cells in atrophied mammary tissue in male mice of a high cancer strain may have the potentialities for tumor development, but few if any tumors occur unless the glandular epithelium is first prepared by estrone.[8] Huseby and Bittner[9] have shown that precancerous nodules appear in mammary tissue prior to cancer formation, and other preneoplastic lesions have been long recognized. It is assumed that the opportunities for neoplastic transformation of normal tissue have been increased considerably during this preliminary period. Thus a "proper soil" appears essential for the genesis of some neoplasms, but there is no reason to believe that such preparation is universally required for all types of tumors. The observation of Mottram[10] that croton oil accelerates tumor formation when applied to the epidermis prior to the application of a carcinogen is contrary to most findings and must be confirmed, and although Simpson and Cramer[3] postulate sensitization as a prerequisite to the genesis of the neoplastic cell, our results indicate that stimulation follows the formation of the tumor cell. Nevertheless, the available evidence, although not conclusive, is sufficient to justify the subdivision of the period of induction of certain tumors into two phases: (*a*) stage of preneoplasia and (*b*) stage of genesis.

2. *Critical Period or Period of Reversibility.*—This starts at the moment at which the genesis of the neoplastic cell has been completed and is that stage in which cellular proliferation is delicately balanced. During this phase there are so few neoplastic cells present that they are more or less lost among the normal cells, and since their mass has not yet attained a size sufficient to receive a direct supply of blood, they must compete with the healthy cells for the nutrients in the fluids of the tissue spaces. At such times these cells are the most susceptible to the influence of their environment; presumably during this phase some tumor cells proliferate, some lie quiescent for varying periods and others succumb. Small nests of tumor cells have less chance of survival than larger clusters,[11] and the fate of small masses of neoplastic tissue depends on the balance between their proliferative capacity and the amount of encouragement or of resistance present in the neighboring tissues. This period could vary from a few hours to several weeks or months.

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8. Gardner, W. U.: Arch. Path. **27**:138, 1939.

9. Huseby, R. A., and Bittner, J. J.: Cancer Research **6**:240, 1946.

10. Mottram, J. C.: J. Path. & Bact. **56**:391, 1944.

11. Reinhard, M. C.; Goltz, H. L., and Warner, S. G.: Cancer Research **5**: 102, 1945.

The concept of a critical period in the development of a tumor is supported by several types of experimental evidence,[2a] but of special consequence is the evidence of a latent period under certain conditions of carcinogenesis. When a carcinogenic hydrocarbon is applied to the skin of mice for a time short of that necessary to induce tumors, the subsequent resumption of the hydrocarbon treatment will quickly precipitate the formation of tumors even though three to four months intervene between the two periods of application of the hydrocarbon.[2a] Actually in certain cases a noncarcinogenic agent, such as heat, a wound or croton oil, may substitute for the hydrocarbon in the second period.[12] Such observations indicate that the initial application of the hydrocarbon produced alterations in the tissues that persisted for at least four months, and we may assume either dormancy of a partially completed chemical reaction which is essential to carcinogenesis and which may be reinitiated and completed by a second application of the carcinogen at some subsequent date, or we may consider that one phase of the carcinogenic reaction, i. e., the genesis of tumor cells, had been completed and such cells remained quiescent until stimulated to proliferation at some later date. Since the concept of an interrupted chemical reaction does not appear too plausible, it seems more likely that the latter suggestion is the more correct. At all events, it is known that tumor cells may persist in a quiescent state for as long as sixteen to twenty-nine weeks before perceptible growth is observed.[13]

The importance of factors that are responsible for the realization of tumors has been mentioned by several authors,[14] but it is our contention that the influence of these forces is most pronounced during the critical period. Gardner[13c] observed that testicular interstitial cell "tumor rests" could be stimulated to proliferation following the injection of estrogens, and the cocarcinogenic influence of most chemical and physical irritants is also most effective when applied subsequent to a period of carcinogenic treatment.[15]. It is also of interest that high calory diets have relatively little stimulative effect during the period when cancer is being initiated or on the growth of established tumors but are definitely stimulative if given just after the preliminary period of carcinogenic treatment, i. e., the critical period.[16]

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12. Berenblum.[1a] Friedewald and Rous.[1b] Kline and Rusch.[2a] Pullinger.[6a]

13. (*a*) Ellinger, F.: Nature, London **142**:151, 1938. (*b*) Fischer, A.: Am. J. Cancer **31**:1, 1937. (*c*) Gardner, W. U.: Cancer Research **5**:497, 1945.

14. Fischer.[13b] Friedewald and Rous.[1b] Kline and Rusch.[2a] Tannenbaum.[2d]

15. Cramer, W.: Brit. J. Exper. Path. **10**:335, 1929. Berenblum.[1a] Friedewald and Rous.[1b] Rusch.[1d]

16. Rusch, H. P.; Kline, B. E., and Baumann, C. A.: Cancer Research **5**:431, 1945.

The length of the critical period, no doubt, varies for different tumors. Neurofibroma developing in the ear of the rat as a result of prolonged feeding of crude ergot regressed when such feeding was discontinued but recurred when the administration of ergot was resumed.[17] This type of tumor cell failed to proliferate in the absence of certain stimulating factors, and the tumor never became autonomous. The anterior chamber of the eye has been shown to be an excellent location for the growth of many types of tumors, and it illustrates a region of favorable environment for the proliferation of tumor cells during the critical period.[18] Once the neoplasm becomes autonomous, its cells may proliferate in a variety of tissues.

3. *Period of Progression.*—This may be considered as that period when the neoplastic cells have gained ascendancy over the forces that hold them in control. The tumor has established its own vascular supply and no longer needs to compete with normal cells for the nutrients in the tissue spaces [2a] but in general is in a period of relatively unrestricted, invasive growth, during which regressions are infrequent. The exact size that a neoplasm must attain before it reaches this stage varies, no doubt, with different tumors, but all grossly perceptible tumors are probably in this phase of their growth. Although there is no sharp line between the second and the third period, there is some evidence in favor of such distinction. As stated previously, Reinhard, Goltz and Warner [11] have shown that the chance of survival of a transplantable mouse adenocarcinoma was proportional to the number of cells inoculated and that the latent period for a tumor "take" increased as the number of injected cells decreased. They have further observed more regressing tumors in animals inoculated with dilute suspensions, while none were seen in mice inoculated with concentrated suspensions. If our point of view is correct, it suggests that all inoculated tumor cells, like spontaneous neoplasms, pass through a critical period before they become established. It seems probable that spontaneous tumor cells face a similar but, most often, more precarious critical period.

The proposed three periods represent only an arbitrary scheme intended to assist in the clarification of our views on carcinogenesis and to facilitate further experimentation. Possibly the different stages are not clearly separable, and within a neoplastic focus at any period tumor cells are being formed, others are dividing and still others are dying. The final outcome is the result of a balance of the various factors involved. At all events, the ability of tumor cells to remain dormant for long periods and to respond to noncarcinogenic stimulation by multiplying

17. Nelson, A. A.; Fitzhugh, O. G.; Norris, H. J., and Calvery, H. O.: Cancer Research **2**:11, 1942.

18. Greene, H. S. N., in Research Conference on Cancer, American Association for the Advancement of Science, 1945, p. 154.

into growth provides an explanation of those clinical instances in which cancer appears after certain injuries of tissues that had previously seemed normal.

SUMMARY

In order to investigate some of the biologic properties of carcinogens and to gain further information on the various stages of cancer formation, methylcholanthrene dissolved either in benzyl alcohol or in wool fat was applied at various periods to the skin of 240 albino mice. Wool fat had a pronounced retarding influence on the formation of cutaneous tumors, and its effect was in direct contrast to the rapid onset of neoplasms observed when benzyl alcohol was used as the solvent for the hydrocarbon. When a solution of methylcholanthrene in wool fat was painted on mice for four months, no visible tumors were found, but when the carcinogen was subsequently applied to the same area in a solution of benzyl alcohol, tumors quickly appeared. The rapidity of appearance of perceptible neoplasms suggested that the carcinogen merely stimulated the proliferation of existing tumor cells during the second period of treatment, a concept which gained further support from the fact that croton oil, a noncarcinogenic substance, could be substituted for methylcholanthrene during the second stage with similar results. Wool fat greatly diminished the effects of both methylcholanthrene and croton oil, a fact implying that it had a neutralizing effect on these tissue irritants.

The results of this experiment suggest at least two biologic characteristics of methylcholanthrene that are essential for tumor development; one is responsible for the genesis of the neoplastic cell, and the other stimulates cellular multiplication. The latter property appears to be the result of nonspecific irritation of tissue. Neoplasms develop only as a consequence of the proper sequential summation of such properties.

Further support is given to the suggestion that tumor formation may be divided into various phases as follows:

1. Period of induction. During this period the neoplastic cell is formed. For certain tumors this phase is further subdivided into a stage of preneoplasia and a stage of genesis.
2. Critical period or period of reversibility. This is a transitional period in which the growth of the cells is in delicate equilibrium with the influence of their environment and depends on the balance between the proliferative capacity of the cell and the local tissue resistance.
3. Period of progression. During this period growth is relatively unchecked.

# Notes and News

**The Scientific Exhibit, Atlantic City Session of the American Medical Association.**—At the Atlantic City Session, June 9 to 13, 1947, the American Medical Association will observe its centennial anniversary. For almost half of those hundred years—since 1899—the Scientific Exhibit has been a feature of each annual session and has developed into a short course in graduate medical instruction.

Exhibits at the 1947 session will cover all phases of medicine. A certain amount of historical material will be included, but emphasis will be placed on the latest developments of medical science. The representative to the Scientific Exhibit from the Section on Pathology and Physiology is Dr. Frank W. Konzelmann, Atlantic City Hospital, Atlantic City, N. J.

Applications for space should be submitted as early as possible, since the closing date is Jan. 13, 1947. Application blanks may be obtained either from Dr. Konzelmann or from the Director, Scientific Exhibit, American Medical Association, 535 North Dearborn Street, Chicago 10.

**Appointments, Etc.**—Frank B. Queen, formerly pathologist at Passavant Hospital, Chicago, and then director (colonel, United States Army) of the laboratories at Bushnell General Hospital, Brigham, Utah, is now professor of pathology in the University of Oregon Medical School. He has charge of the tumor clinic of the school and directs the activities of the Oregon division of the American Cancer Society.

R. D. Johnston, recently on duty in the Army Institute of Pathology, has been appointed assistant professor of pathology in the University of Oregon Medical School.

Brigadier General Standhope Bayne-Jones has resumed work at Yale University as professor of bacteriology and director of the Jane Coffin Childs Memorial Fund for Medical Research.

At Northwestern University Medical School J. P. Simonds has become professor of pathology emeritus. His successor is William B. Wartman, formerly assistant professor of pathology in Western Reserve University. Thomas C. Laipply, also assistant professor at Western Reserve University, has been appointed associate professor of pathology at Northwestern University.

F. B. Johnson has resigned as professor of clinical pathology at the Medical College of the State of South Carolina.

At the University of Washington School of Medicine, Seattle, a department of microbiology has been established, which includes bacteriology, immunology, virology, mycology and medical protozoology. The director is Charles A. Evans, associate professor of bacteriology and immunology, University of Minnesota.

**Death.**—Ward J. MacNeal, professor of bacteriology at the New York Post-Graduate Medical School and Hospital, Columbia University, died Aug. 15, 1946, 65 years old.

**Awards.**—Anton J. Carlson, professor emeritus of physiology at the University of Chicago, received the Distinguished Service Medal of the American Medical Association at its recent meeting in San Francisco.

The Ward Burdick Medal of the American Society of Clinical Pathologists has been awarded to A. S. Wiener and Philip Levine for their work on the Rh factor.

The Trudeau Medal of the National Tuberculosis Association has been awarded to Max Pinner, Berkeley, Calif., for his contribution to the control of tuberculosis.

The Walker prize of the Royal College of Surgeons is awarded every five years "to the person, if any, who shall be deemed to have done the best work during the preceding five years in advancing the knowledge of the pathology and therapeutics of cancer." The prize for the years 1936 to 1940, inclusive, was awarded to F. P. Rous, of the Rockefeller Institute for Medical Research, who received it on July 10 last, when he lectured on antecedents of cancer (*Lancet* **2**:98, 1946).

**American Board of Pathology.**—A. H. Sanford, Rochester, Minn.; Frank Hartman, Detroit; Frederick Lamb, Davenport, Iowa, and J. J. Moore, Chicago, have retired after twelve years of service. New members of the board are: J. A. Kasper, Detroit; James Kernohan, Rochester, Minn.; Edwin Schultz, San Francisco. The other members of the board are: Shields Warren, Boston; N. C. Foot, New York; R. P. Custer, Philadelphia; William Sunderman, Philadelphia; Paul Cannon, Chicago; James McNaught, San Francisco; R. A. Moore, St. Louis. N. C. Foot is the president; M. Sunderman, vice president, and R. A. Moore, secretary-treasurer. The next examination will probably be held in Philadelphia about June 1, 1947. Inquiries should be sent to Dr. R. A. Moore, Washington University School of Medicine, St. Louis 10.

**Finney-Howell Fellowships.**—Applications for 1947 must be filed by January 1 next (1211 Cathedral Street, Baltimore). The awards will be made March 1, 1947. The purpose of the fellowships, each $2,000 a year, is to support research into the causes and the treatment of cancer in places approved by the directors.

**National Institute of Health.**—The first session of the pathology study section of the institute's research grants division was held Aug. 16, 1946. This section, which is one of more than twenty groups of consultants advising in the whole field of medical research, is composed of Paul Cannon, chairman; W. S. DeMonbreun, W. H. Feldman, W. D. Forbus, H. Goldblatt, J. S. McCartney, A. R. Moritz, A. Rich, J. F. Rinehart, H. P. Smith, representatives of the Surgeons General of the United States Army, the United States Navy and the medical department of the Veterans Administration, and R. D. Lillie, National Institute of Health, Bethesda, Md., executive secretary.

Application forms for grants in aid may be obtained by addressing the Chief, Research Grants Division, National Institute of Health, Bethesda 14, Md. For prompt action applications should be filed well in advance of the quarterly meetings of the study section concerned.

# Books Received

LE REIN POLYKYSTIQUE: ETUDE MORPHOLOGIQUE, CLINIQUE ET PHYSIOPATHOLOGIQUE. By P. P. Lambert, Clinique médicale Hôpital universitaire Saint-Pierre (Prof. Paul Govaerts) et Laboratoire d'Histologie, Université de Bruxelles (Prof. P. Gérard). Preface by Prof. Paul Govaerts. Pp. 140. Paris: Masson & Cie, 1943.

After a review of previous studies, mainly concerned with cystic kidney of the newborn, the author reports the results of an extensive and comprehensive morphologic study of the polycystic kidney of the adult. Because of technical difficulties, this subject had been incompletely studied previously.

The cysts are classified into three types: (*a*) the glomerular cysts, which are "closed cysts," (*b*) the tubular cysts and (*c*) the cysts of the collecting tubules. By serial sections and graphic reconstruction, the author shows that in the adult most of the cysts of the last two types are open cysts, while in the newborn they are closed cysts.

If it is assumed that there is no pathogenic difference between the cystic kidney of the newborn and that of the adult, the theory of absence of union between the metanephric and the ureteral parts of the nephron is refuted. Contrary to the views of some investigators, retention is not considered as playing a role in the formation of the cysts. The cysts are probably the cause of the failure of the two parts of the nephron to become united but are not the result of that failure. In the newborn most of the cysts are "closed cysts" because the cystic degeneration occurs before the union of the two parts of the nephron. In the adult they occur in an otherwise well developed nephron. The author, however, does not explain the pathogenesis of the primary cystic degeneration of the nephron.

The second part of the book comprises the results of a chemical analysis of the contents of the cysts of the kidneys. As judged by means of an intraperitoneal injection of inulin, it seems that most cysts in the adult are connected with a normally functioning glomerulus. The author believes, contrary to the opinion of other investigators, that the epithelium lining the tubular cysts still conserves its physiologic functions. This book, though somewhat controversial, is an interesting and stimulating study of the polycystic kidney.

RENAL HYPERTENSION. By Eduardo Braun-Menendez, Juan Carlos Fasciolo, Luis F. Leloir, Juan M. Munoz and Alberto C. Taquini, Institute of Physiology, Faculty of Medical Sciences and Institute of Cardiology, V. F. Greg Foundation, Buenos Aires, Argentina. Translated by Lewis Dexter, M.D., Harvard Medical School and Peter Bent Brigham Hospital, Boston. Pp. 451, with 93 illustrations. Price $6.75. Springfield, Ill.: Charles C Thomas, Publisher, 1946.

This volume is an excellent and complete review of the significant literature in the field of experimental and clinical renal hypertension by a group of Argentinian investigators who have contributed most importantly to the subject under the early stimulus of the famed physiologist Dr. Bernardo A. Houssay. Since the authors' interpretations of the available experimental and clinical evidence largely agree with the majority views of authorities, the book constitutes a sound summary of present knowledge of renal hypertension. This first English edition has been most competently translated by Dr. Lewis Dexter, whose qualifications for the task include a period of scientific collaboration with the authors, as well as independent contributions to the subject.

The chapter divisions present the matter in a logical sequence from the methods of producing permanent experimental hypertension (including the classic work of

Goldblatt) to the relationships between experimental and clinical renal hypertension. Included are chapters on: the pathophysiology and the pathogenetic mechanisms of experimental renal hypertension; the chemical, physiologic and pharmacologic properties of the renin–hypertensinogen–hypertensin–hypertensinase system and its relation to experimental renal hypertension; the protective action of the so-called normal kidney; the influence of the endocrine glands, and the role of other vasoconstrictor substances, including pressor amines. The authors offer a challenging classification of human hypertension, followed by chapters dealing with hypertensions of renal or probably renal origin and more importantly with essential and malignant hypertensions (which are classified as of possible renal origin). One chapter each is devoted to methods of medical and surgical treatment, which are conservatively and fairly evaluated.

Each chapter includes a concise summary, which should prove convenient to the reader who is new to the field and to the clinician who may wish to read in brief the early chapters devoted to experimental hypertension and in detail the later chapters concerned with clinical hypertension. An appendix of chemical and biologic methods useful to investigators and an inclusive yet selective bibliography complete this dynamic, vibrant volume, which should be read by all interested in the problem of hypertension.

PENICILLIN: ITS PRACTICAL APPLICATION. Under the general editorship of Prof. Sir Alexander Fleming, M.B., B.S., F.R.C.P., F.R.C.S., F.R.S., professor of bacteriology in the University of London, St. Mary's Hospital, London. Pp. 380, with 59 illustrations. Price $7. Philadelphia: The Blakiston Company, 1946.

Here are six articles of a general nature about penicillin and twenty-one about different aspects of penicillin treatment, including its use in human dental and oral infections as well as in animal infections, all by British workers. Of the contributors of general articles, Fleming himself writes about the history and the development of penicillin and about the bacteriologic control of penicillin therapy. These articles and the preface have of course a very special interest. The other general articles deal with the pharmaceutic and the pharmocologic aspects and the methods of administration of penicillin. The illustrations are telling. The book gives an excellent conspectus of penicillin therapy as it exists today.